Abstract

Objectives

To assess the cost effectiveness of basal insulin regimens for adults with Type 1 diabetes (T1D) in England.

Methods

Cost-utility analysis (CUA) was undertaken in accordance with NICE reference case. UK NHS and personal and social services (PSS) perspective was used and 3.5% discount rate applied for both costs and outcomes. Relative effectiveness estimates were based on a systematic review of published trials and a Bayesian network meta-analysis (NMA). The IMS CORE Diabetes Model (CDM) was used, where net monetary benefit (NMB) was calculated using a threshold of £20,000 per quality-adjusted life-year (QALY) gained. Wide range of sensitivity analyses was undertaken.

Results

Insulin detemir (twice-daily) [iDet (bid)] had the highest mean QALY gain (11.09 QALYs) and NMB (£181,456) per patient over the model time horizon. Compared to the lowest cost strategy (insulin NPH once daily [iNPH (od)]; it had an incremental cost-effectiveness ratio (ICER) of £7,844 per QALY-gained. Insulin glargine (od) [iGlarg (od)] and iDet (od) were ranked as second and third, with NMB of £180,893 and £180,423, respectively. iDet (bid)] remained the most cost-effective treatment throughout the sensitivity analyses performed except when high doses were assumed (>30% increment compared to other regimens); where in this scenario analysis iGlarg (od) ranked first.

Conclusions

iDet (bid) is the most cost-effective regimen; providing the highest QALY gain and NMB. iGlarg (od) and iDet (od) are possible options for those for whom the twice daily regimen of insulin determir is not acceptable or does not achieve required glycaemic control.

Introduction

Type 1 diabetes mellitus (T1D) is a long-term hormonal deficiency disorder, caused by autoimmune destruction of the insulin-secreting beta cells of the pancreas. This results in high plasma glucose concentrations and other metabolic and haematological abnormalities, which have both acute and long-term adverse effects. (1) Over the long term, T1D carries risk of major complications and reduced life expectancy. (2)

Approximately 10% of adults diagnosed with diabetes have T1D. (3) In 2010-2011, the cost of T1D to the National Health Service (NHS) was estimated to be around £1 billion, with around 80% due to complications. (3) At present there is no cure. The treatment of T1D is insulin replacement therapy and this insulin is not under endogenous control. Insulin regimens that reduce and improve the stability of glycated haemoglobin (HbA_{1c}), a reflection of average plasma glucose concentrations over the medium term (two to three months), are likely to reduce short-term complications such as hypo- and hyperglycaemia and also to reduce the occurrence of long-term complications and premature mortality.(4-6)

Basal insulin replacement needs to provide glucose control between meals and overnight, with minimal risk of hypoglycaemia. An insulin that has a long and flat duration of action is expected to be optimal for basal replacement, and minimising the numbers of injections required to provide basal cover that reliably lasts at least 24 hours is desirable. Current basal insulin regimens in common use in the United Kingdom (UK) include the human intermediate acting insulins, such as the isophane or Neutral Protamine Hagedorn (iNPH) insulins (human, porcine or bovine); the insulin analogues insulin detemir (iDet) and insulin glargine (iGlarg), which have flatter 'peakless' insulin action profiles, (7;8) and more recently the very long-acting insulin insulin degludec (iDegl).(9) Each new basal insulin analogue has data to suggest less day to day variability than earlier insulins and more prolonged duration of action,(10;11) with most expensive basal insulin replacement (iDegl) showing particularly low variation and long duration of action.(9) Increased cost of the newer insulins, especially insulin iDegl, needs to be balanced against potential improvement in glycaemic control and risk of hypoglycaemia.

There is evidence that, at least in some people, neither iNPH nor iDet nor iGlarg provide 24 hour glucose control with a once-daily injection,(12;13) and because of stress laid on flexibility of basal

dosing in structured education programmes such as Dose Adjustment For Normal Eating (DAFNE), twice-daily basal regimens are increasingly used in clinical practice.(14) Existing economic evaluations of basal insulin regimens give conflicting results in terms of the relative cost-effectiveness of basal insulin regimens. The most recent review of published economic evaluations of long- and intermediate-acting insulin regimens identified 5 economic evaluation studies comparing iNPH with iDet.(15-20) Three found that iDet was less costly and more effective; .(17-19) while the other two found that iDet was more costly and more effective. Similarly, conflicting results were found for the comparison of iNPH with iGlarg (16;20) None of these studies evaluated iDegl; none compared all basal insulin regimens and importantly, none have considered the frequency of daily injections of each insulin. Hence, the economic analysis reported in this paper was undertaken to fill the evidence gap relative to assess tthe cost effectiveness of all clinically relevant basal insulin regimens available for adults with T1D in England; ,the analysis was used to inform the choice of the optimal basal insulin regimen to be recommended in the NICE Clinical Guideline NG17 . Insulin glargine 300 IU was not available in the UK at the time this work was conducted, so is it was not included.

Methods

This CUA was conducted from the perspective of the NHS and Personal Social Services (PSS), with quality-adjusted life-years (QALYs) and costs as the main outcome measures. The analysis complied with the NICE Reference Case, which is a set of methodological standards specified by NICE including using lifetime time horizon and applying discounting at a 3.5% discount rate for both costs and QALYs, for costs and outcomes accrued beyond the first year. (21) The reporting also follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. No ethics approval was required for this study.

Comparators

The following insulin regimens were compared against each other: iDet (once daily) (iDet (od)), iDet (twice daily) (iDet (bid)), iGlarg 100 IU (once daily) (iGlarg (od)), iDegl (once daily) (iDegl (od)), iNPH (once daily) ((iNPH (od)), iNPH (twice daily) ((iNPH (bid)), iNPH (four times daily) ((iNPH (qid)). An average daily dose was assumed for all comparators (24 units).(22) This was assumed to be given in divided doses for comparators with more than once daily dosing frequency.

Model description

The analysis was undertaken using the IMS CORE Diabetes Model (CDM) Version 8.5.

The model simulates diabetes progression using a series of interlinked, inter-dependent sub-models of the following diabetes complications: angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and non-specific mortality.

These sub-models are Markov models which use time-, state- and diabetes type-dependent probabilities that have been derived from published sources. Interaction between the individual complication sub-models is mediated through the use of Monte Carlo simulation using tracker variables. Full description of the CDM and its modules and sub-models is given in Palmer et al (2004).(23) The model has been validated extensively against epidemiological and clinical studies of type 1 diabetes.(24)

The model input parameters are grouped into the following databases: cohort, economics, other management, clinical, treatment (clinical effectiveness, costs). The default inputs for T1D were validated with the members of the NICE guideline development group (GDG), however, where more reliable or recent UK sources were identified through our systematic and/or targeted literature reviews, these were used instead. The details of the model parameter inputs used in the analysis and their references are provided in the supplementary materials, part 1.(25)

Simulation cohort

For the CDM, the population cohort was defined in terms of age, gender, baseline risk factors and pre-existing complications, using data that reflected a UK-based, adult, T1D population (Table 1). Baseline complications were assumed nil unless reliable UK data could be identified (for example for stroke and angina).

Insert Table 1: Cohort Characteristics

Treatment effects

Two outcomes were used to characterise treatment effects: change in HbA_{1c} from baseline (expressed as percentage) and rate of severe hypoglycaemic events.

Treatment effects for both outcomes were based on a systematic review and network meta-analysis (NMA) published separately. Twenty-eight RCTs were included in the review. Two networks were constructed and analysed, one for change in HbA1c (25 studies generating 27 comparisons) and one for severe/major hypoglycaemic events (16 studies generating 16 comparisons). The included studies were systematically identified, assessed and reviewed. The details of the review and NMAs have been reported separately. (32) In all included trials, the same bolus insulin was used in both treatment arms.

For the first outcome, change in HbA_{1c}, the mean treatment effect (Table 2) was applied to the cohort baseline HbA_{1c} value (8.6%) to specify the level of HbA_{1c} achieved when using each of the insulin regimens. The regimen-specific mean rate of severe/major hypoglycaemic events was obtained from the NMA results (Table 2). No trials were identified which reportd this outcome for iNPH (qid) therefore, iNPH (qid) was assumed to have the same mean event rate as iNPH (bid). This assumption was tested in a sensitivity analysis.

Insert Table 2: Treatment effects

Costs

Only direct costs, i.e. costs of treatment, complications, and diabetes management, were included in the analysis. The CDM defaults were updated to reflect current UK costs and clinical practice, where appropriate. All costs from sources published before 2013 were inflated to 2013 using the 2012/13 Hospital and community health services (HCHS) index.(33)

For treatment costs, only the insulin and needles' costs were considered as being likely to differ among the comparator regimens. The costs of monitoring, nurse time and other consumables were considered to be either the same or negligibly different and were not included. Insulin costs were calculated using nationally available prices from the British National Formulary (BNF) and MIMS June 2013,(34) (35) assuming that only cartridges or pre-filled pens were used. An average price was calculated for cartridges' and pre-filled pens' prices if these were different.

The cost of needles, calculated as a weighted average based on the prices of the 10 most commonly used needles was £0.11 per needle. (36) The annual treatment cost per patient was calculated as the sum of the insulin and the needles' cost (Table 3).

Insert Table 3: Treatment costs

Quality of life (QoL)

In the CDM, patients with T1D in the absence of complications experience a QoL of 0.814 on a scale from 0 to 1. Other events and complications occurring in the model are associated with specific QoL (e.g. chronic heart failure, retinopathy, depression, etc) and one-off QoL decrements (e.g. myocardial infarction, stroke, etc). The default QoL values of the CDM were used, with the exception of the QoL value associated with major hypoglycaemic events, which required adjustment to calculate the disutility per episode. This was calculated to be -0.012.(38) All utility and disutility values used are listed in the Supplementary material, part 1, Table 2.

Probabilistic analysis

The base case analysis was run deterministically and probabilistically. The probabilistic analysis was undertaken to assess the impact of parameter uncertainty on the model results, where input parameter values were randomly sampled simultaneously using Monte Carlo simulation from relevant distributions that are default to the CDM (see Palmer et al (2004) for detail of the distributions used.(23) It was not possible, however, to preserve the correlations between the strategies' relative effectiveness estimates obtained from the NMA as the CDM is not equipped to sample from NMA posterior distribution.

Cost-effectiveness acceptability curves (CEACs) were also constructed to assess decision uncertainty; where the probability of being the most cost-effective strategy was plotted against cost-effectiveness threshold values ranging from £0 to £100,000 for each of the included strategies.

Sensitivity analysis

In addition to the probabilistic analysis, deterministic sensitivity analyses (SAs) were undertaken to test the robustness of the model results to changes in assumptions and inputs. In each SA, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether

conclusions on which intervention should be recommended would change. Details of the analyses SA1 to SA8 are provided in Panel 1.

Panel 1: details of the sensitivity analyses

SA1 - HbA_{1c} progression
In the base case analysis, the CDM default value for the annual progression in HbA_{1c} was used (0.045%). An alternative assumption of no annual progression in HbA_{1c} level (0%) was tested. This was done because, in contrast to the case in type 2 diabetes, there is no life-long increase in insulin deficiency in T1D, after completion of the honeymoon phase. .

SA2 - Utility estimation approach
In the base case analysis, the CDM default "minimum approach" to calculating utility was used. In this approach, the quality of life for patients with multiple complications is assumed to take the minimum of the utility values associated with these complications. An alternative "multiplicative approach" was tested whereby utility for these patients is calculated as a multiplicative function of the utilities for these complications.

SA3 - Rate of severe/major hypoglycaemic events
In the base case analysis, the rates of severe/major hypoglycaemic events were based on the treatment-specific data from the NMA. Since there was a lot of uncertainty around this outcome and the NMA did not show any significant difference in hypo event rates between treatments, in a sensitivity analysis we assumed no differential effect for any of the comparators on hypoglycaemic event rate, effectively considering HbA_{1c} as the only clinical effectiveness outcome measure. The rate used for all the treatment was that of iNPH (bid) (35 events per 100 patient-years).

SA4 - Cohort characteristics

In the base case analysis, the simulated cohort represented the average population with T1D in the UK. A scenario analysis was run assuming a cohort representing a population in the UK with a more recent diagnosis of T1D. The alternative cohort characteristics are reported in the table below.

Cohort characteristics in SA4

Input variable	**Value**
Start age (years)	27
Duration of diabetes (years)	9.10
Proportion Male	55.2%
HbA_{1c} (-points)	9.3%
Systolic Blood Pressure (mmHg)	121.48
Body mass index (BMI) (kg/m^2)	24.90
Proportion smoker	26%

SA5- Cost of major hypoglycaemic events
The cost of a major hypoglycaemic event used in the base case analysis was based on the study by Hammer et al (2009)(39) and was estimated to be £333. This was examined in a sensitivity analysis where the cost was varied between £0 and £500.

SA6 - Utility of major hypoglycaemic events
The base case value (-0.012) was based on an adjustment made to the value reported in the study by Currie et al (2006).(38) The original higher value of -0.047 has been used in our one-way sensitivity analysis..

SA7 - Mortality of major hypoglycaemic events
The base case mortality due to severe/major hypoglycaemia was varied in a one-way sensitivity analysis within a range between 0% and 5%.

SA8 - Discounting
The discount rate was varied to 1.5% for both costs and benefits.

SA9: Insulin doses
Regimen-specific daily dose was calculated based on data from the RCTs included in the NMA rather than assuming an average dose of 24 units (supplementary material, part 2).

SA10: iDet (bid) dose
A threshold analysis in which the dose of iDet (bid) was increased relative to other regimens in 5% increments, between 105% and 140%, based on the assumption that it is weaker insulin, was also carried out.

Statistical approach

The CDM was run probabilistically, with probability distributions defined for each parameter, to take account of the uncertainty around the point estimates of the input parameters. In each run, a value for each input was randomly selected simultaneously from its respective probability distribution and means for costs and QALYs were calculated. The analysis was run repeatedly (1000 times) for the base case and results were summarised. Distributions around different parameters are set by default in the model and these are explained in the document available on the CDM website.(40)

The results were presented in terms of net monetary benefit (NMB), (41) calculated by multiplying the total QALYs for a comparator by the cost-effectiveness threshold defined by NICE (£20,000/QALY gained) and then subtracting the total costs (formula below). The decision rule applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. This is the option that provides the highest number of QALYs at an acceptable cost. Results are also presented graphically; where total costs and total QALYs for each regimen are shown on a cost-effectiveness plane. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio (ICER). (41)

$Net\,Monetary\,Benefit(X) = (QALYs(X) \times \lambda) - Costs(X)$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost-effective if: Highest net benefit

Two T1D patients were members in the GDG and contributed to the design, planning and validation of model inputs and assumptions. The analysis methods and results were regularly presented to and validated by all of the GDG including the two patient members.

Results

The results of the base case probabilistic analysis are presented in Table 4. These show that the optimal strategy at a cost-effectiveness threshold of £20,000 per QALY was iDet (bid), which was also the most effective strategy (highest mean QALYs gained). This strategy was dominant, i.e. it was more effective and less costly, compared to two strategies: iDegl (od) and iNPH (qid), it was more effective and costly than iDet (od), iGlarg (od), iNPH (od) and iNPH (bid) and a cost-effectiveness

threshold of £20,000 per QALY gained, the increased effectiveness justified the increase in costs. The incremental analysis results show that iDegl (od), iNPH (qid), iNPH (bid) and iDet (od) were dominated strategies. iGlarg (od) was extendedly dominated by a combination of iNPH(od) and iDet (bid); however if iDet (bid) were not available, the probabilistic ICER of iGlarg (od) compared to iNPH (od) would be £8,605 per QALY, hence iGlarg(od) would be the preferred option. Excluding the dominated options, the probabilistic ICER of iDet (bid) vs iNPH (od) was £7,844 per QALY (Figure 1).

Insert Table 4: Probabilistic base case analysis results

The CEACs showed that, at cost effectiveness threshold of £20,000 per QALY gained, iDet (bid) had the highest probability of being cost effective (26%). This increased to 41% for a cost effectiveness threshold of £30,000 per QALY gained and reached a maximum of 42% for threshold values >£30,000 per QALY gained (Figure 2).

The breakdown of the life-time costs per patient shows that the use of iDet (bid) generated a mean direct cost higher than use of iGlarg (od), iNPH (bid), iNPH (od) and iDet (od). This was mainly driven by the higher cost associated with treatment (£5,074) and longer survival. However, the total costs of treating renal complications, ulcer/amputation/neuropathy and eye-related complications were lower when using iDet (bid) compared to other insulin regimens. In fact, the use of iDet (bid) was associated with the lowest cost across all comparators in these categories and in the total cost of managing all complications (£32,115). This is likely to be due to the better control of HbA_{1c} achieved with iDet (bid). The total cost of using iDegl (od) was the highest among the 7 comparators, driven by the highest treatment cost (£7,169).

The SAs' results (supplementary material, part 2) showed that the model was robust to many changes in input parameters in terms of the best ranking strategy. This was the case for SAs 1 to 9. Changing the utility estimation approach (SA2) and the discount rate (SA7) did not lead to any other change in the ranking of any of the strategies compared to the base case.

SA1 (assuming no annual progression in HbA1c), SA3 (changing the rate of severe/major hypoglycaemic events), SA4 (changing cohort characteristics), and SA5 (the cost of major/severe hypoglycaemic events was assumed to be £0) resulted in changing the relative ranking of iNPH (od) and iNPH (bid), with iNPH (bid) ranking higher than iNPH (od).

When mortality of major hypoglycaemic events was assumed to be 5% (SA7) and when the doses were based on the RCT doses (SA9), the relative ranking of iDet (od) and iGlarg (od) changed; with iDet(od) ranking higher than iGlarg (od). The results of SA10 (supplementary material, part 2), showed that while keeping the dose of other insulin regimens to the base case value of 24 units per day, the dose of iDet (bid) would have to increase by 30-35% of the base case value for this regimen to switch its ranking with iGlarg (od). If this dose is further increased (by 40%), iDet (bid) would be ranked third, after both iGlarg (od) and iDet (od), which would rank first and second, respectively.

Discussion

The base case probabilistic analysis results, as well as those of all SAs, show that iDet (bid) is the most clinically effective basal insulin replacement regimen, with the highest mean QALYs gained over life-time time horizon. It was the also the optimal choice in terms of cost-effectiveness, with the highest NMB compared with all other long-acting insulin regimens. This was confirmed in all the SAs conducted, except when much higher doses were assumed to be required (30% or more compared to other regimens). Thus, the cost effectiveness of iDet (bid) over iGlarg (od) remained true until the required dose of iDet (bid) is more than 125% that of iGlarg (od). The average difference in dose estimated from the RCTs included in the NMA was 111%, which is well within this limit.

iGlarg (od) ranked second in the base case analysis, while iDet (od) was extendedly dominated (i.e. was less cost effective than a combination of two other regimens). However this ranking changed in two SAs: when using the long-acting insulin regimen daily dose from the RCTs (SA9) and when the mortality from major hypoglycaemic events was increased to 5% (compared to 0% in the base case, SA7). In both these SAs, iDet (od) ranked second followed by iGlarg (od). In the former analysis (SA9), this change in ranking resulted from a change in the ICER of iGlarg (od) compared to iDet (od) which was calculated to be £28,500 per QALY gained, slightly above the NICE cost-effectiveness threshold of £20,000 per QALY gained, creating some uncertainty around the superiority of iGlarg (od) over iDet (od) in terms of cost effectiveness.

Results from published economic evaluations report conflicting results in relation of the relative cost-effectiveness of basal insulin regimens, with five cost-utility analyses (CUAs) showing that iDet was cost effective compared to iNPH at a cost-effectiveness threshold of £20,000 per quality-adjusted life-year (QALY) gained, (18;20;42-44) while another found that iDet was not cost effective. (16) Three

CUAs found that iGlarg was cost effective compared to iNPH,(45-47) another found that iGlarg was dominant compared to iNPH,(48) while another found that iGlarg was not cost effective compared to iNPH.(16) One CUA found that iDet was dominant (less costly and more effective) over iGlarg, (44) while another found that iGlarg was the dominant option when compared to iDet.(16)

The results of our economic analysis are in line with the findings from some of these previously published cost-utility analyses, which found that iDet was cost effective compared to iNPH (ICERs: £2,500, £3,443, £9,526, £12,989 and £19,285 per QALY gained),(18;20;42-44) iGlarg was cost effective compared to iNPH (ICERs: £3,496 - £4,978, £3,189 - £9-767 and £10,903 per QALY gained),(45-47) and one study finding that iDet was dominant (less costly and more effective) over iGlarg. (44) However, this last analysis and ours conflict with that of Cameron and colleagues, (16) which concluded that iGlarg dominated iDet. This is likely to be due to two main reasons. The first is the fact that drug prices in Canada are very different from those in Europe. The ratio of cost between iDet or iGlarg and NPH and similarly the ratio of cost between iDet and iGlarg are much higher in Canada than in UK. The second is the difference in the clinical effectiveness evidence used to inform the models in the two studies. In Cameron and colleagues' analysis,(16) the clinical effectiveness estimates used in the model were based on a direct meta-analysis (MA) combining results from trials that compared each of iGlarg and iDet versus iNPH. This MA showed that iGlarg was more effective than iDet in terms of HbA_{1c} reduction (-0.11% versus -0.06%, respectively, compared to iNPH but did not consider iDet (od) and iDet (bid) regimens separately. In contrast, our economic analysis utilises clinical effectiveness estimates from our NMA which took into account iDet frequency of administration and provided estimates of relative treatment effects for all 7 basal insulin regimens. To our knowledge, our study is the first original economic analysis to assess the comparative cost effectiveness of the different frequencies of basal insulin administration.

Our study had some limitations. There is, inevitably, uncertainty around some of the model parameter inputs. However, the model results were tested in a wide range of SAs which showed consistent results for the optimal choice [iDet (bid)], with less certainty around the choice of iGlarg (od) and iDet (od) as the second and third best options. We were also not able to include the impact of the insulin regimens on minor hypoglycaemia, defined as episodes of hypoglycaemia that does not require assistance from third party, and body weight due to the lack of a coherent estimate effect to use in

populating the model. It is also not clear how minor hypoglycaemia impacts on health related quality of life. There were also some limitations of the CDM used. In version 8.5, there is no possibility of including nocturnal hypoglycaemia as an outcome when characterising treatment effects. This has been addressed in the latest release (version 9.0). The model also includes parameters that are not specific to a T1D population, utilising some data from the T2D population. Where data were available, we modified the CDM to use T1D data. Reduction in HbA_{1c}, which is the main outcome measure of the CDM, is an intermediate outcome; however; it is considered to be a reliable proxy measure of disease progression and complications. Its link to the most important clinical outcomes for diabetes patients, including complications and mortality is well established and validated. (2;5) Patient adherence and possible disutility due to multiple daily injections were not included in the model as it was believed that adults with T1D generally tolerate increased injection frequency if this provides better control of their diabetes and reduced risk of hypoglycaemia, with no negative effect on the treatment adherence or quality of life.(49) This was confirmed with the patient members of the GDG. Adults with T1D already use multiple injections of short acting insulin and it is not anticipated that there would be further disutility associated with increased frequency of basal insulin administration.

Disutility due to fear of hypoglycaemia was also not explicitly included in the model. However, the utility value associated with suffering a major hypoglycaemic event already incorporates this disutility.(38) A further limitation of the CDM in relation to this model is that it does not have the ability to use the simulation results from the NMA in the probabilistic analysis runs. This is important as independent sampling from the NMA could lead to implausible sets of parameters in some PSA runs. Finally, this original economic analysis is directly applicable to the adult T1D population in England. Generalisability of its findings to the paediatric population or T1D populations in other settings may not be appropriate.

Our results suggest that further research is needed to reduce the uncertainty around the estimates of disutility and mortality associated with severe hypoglycaemic events, given the sensitivity of the model results to these parameters. Nevertheless, this analysis provides a hierarchy for currently available basal insulin regimens in terms of their cost effectiveness, which can guide prescribing decisions and be used to inform NICE guideline recommendation regarding the choice of an optimal regimen for patients in England.

Conclusion

This study showed that, from the perspective of the English NHS, iDet (bid) is the most cost-effective basal insulin regimen for people with T1D, within the range of basal insulin doses seen in clinical trials. iGlarg (od) or iDet (od) are likely to be cost effective for patients for whom iDet (bid) is not an option. This is the first study to assess the relative cost effectiveness of different frequencies of administration of the same insulin.

Author contribution

DD contributed to the study design and acquisition of data, undertook the analysis, contributed to the interpretation of results and wrote the manuscript. EF contributed to the study design, the acquisition and analysis of data and interpretation of the results. DW contributed to the study design, the analysis of data and interpretation of the results. BH and SA contributed to the study design, acquisition of data and interpretation of results. All authors revised the manuscript critically and approved its submission.

Funding

This work was undertaken by the National Guideline Centre (NGC), Royal College of Physicians London (formerly National Clinical Guideline Centre [NCGC]) which received funding from the National Institute for Health and Care Excellence (NICE). The views expressed in this publication are those of the authors and not necessarily those of the Institute. The funding body (NICE) did not play any direct role in the study design; the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. All researchers involved in this work were independent from the funding body at the time of completing this work. All authors, external and internal to the NGC, had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

(1) Max Andersen ML, Nielsen LB, Svensson J, et al. Disease progression among 446 children with newly diagnosed type 1 diabetes located in Scandinavia, Europe, and North America during the last 27yr. Pediatr Diabetes 2014;15(5):345-54.

(2) Nathan DM, McGee P, Steffes MW, et al. Relationship of glycated albumin to blood glucose and HbA1c values and to retinopathy, nephropathy, and cardiovascular outcomes in the DCCT/EDIC study. Diabetes 2014;63(1):282-90.

(3) Diabetes UK. The cost of diabetes: report. 2014.

(4) Lachin JM, Orchard TJ, Nathan DM, DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014;37(1):39-43.

(5) Lachin JM, White NH, Hainsworth DP, et al. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015 Feb;64(2):631-42.

(6) Orchard TJ, Nathan DM, Zinman B, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015 Jan 6;313(1):45-53.

(7) Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes 2000;49(12):2142-8.

(8) Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care 2005 May;28(5):1107-12.

(9) Heise T, Hermanski L, Nosek L, et al. Insulin degludec: Less pharmacodynamic variability than insulin glargine under steady state conditions. Diabetologia 2010;53(Suppl.1):S387.

(10) Heise T, Nosek L, Rã¸Nn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004;53(6):1614-20.

(11) Renard E, Dubois-Laforgue D, Guerci B. Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: A multicenter, randomized, crossover study. Diabetes Technol Ther 2011;13(12):1213-8.

(12) Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with type 1 diabetes using meal-time insulin aspart. Diabet Med 2006;23(8):879-86.

(13) Le Floch JP, Lévy M, Mosnier-Pudar H, et al. Comparison of once- versus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT). Diabetes Care 2009;32(1):32-7.

(14) Amiel S, Beveridge S, Bradley C, et al. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ (Online) 2002;325(7367):746-9.

(15) Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ (Online) 2014 Oct 1;349.

(16) Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. Can Med Assoc J 2009;180(4):400-7.

(17) Valentine WJ, Jendle J, Saraheimo M, et al. Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands. Diabet Med 2012;29(3):303-12.

(18) Valentine WJ, Aagren M, Haglund M, et al. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scand J Public Health 2011;39(1):79-87.

(19) Gschwend MH, Aagren M, Valentine WJ. Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries. J Med Econ 2009;12(2):114-23.

(20) Tunis SL, Minshall ME, Conner C, et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis. Curr Med Res Opin 2009;25(5):1273-84.

(21) National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence, 2012.

(22) Jorgens V, Berchtold P, Berger M. [Therapy of insulin-dependent diabetes mellitus. Regular metabolic control and insulin dose adaptation by the patient]. Deutsche medizinische Wochenschrift (1946) 1979 Dec 21;104(51):1796-8.

(23) Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1

and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin 2004;20(S1):S5-S26.

(24) McEwan P, Foos V, Palmer JL, et al. Validation of the IMS CORE Diabetes Model. Value Health 2014 Sep;17(6):714-24.

(25) National Clinical Guideline Centre. Type 1 diabetes in adults: diagnosis and management. NICE guideline 17. Appendix N: Cost-effectiveness analysis: Longacting insulin and insulin regimen. London: National Clinical Guideline Centre; 2015.

(26) Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med 2009 Jul 27;169(14):1307-16.

(27) The National Diabetes Audit 2011-2012 Report 1: care processes and treatment targets. Leeds: Health and Social Care Information Centre; 2013.

(28) Office for National Statistics. Opinions and lifestyle survey: smoking habits amongst adults, 2012. London: Office for National Statistics; 2013.

(29) World Health Organization. Global status report on alcohol 2011. Geneva: World Health Organization; 2011.

(30) Health and Social Care Information Centre. Health survey for England, 2011: cardiovascular disease. Leeds: The Health and Social Care Information Centre; 2011.

(31) Hopkins D, Lawrence I, Mansell P, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 2012 Aug;35(8):1638-42.

(32) National Clinical Guideline Centre. Type 1 diabetes in adults: diagnosis and management. NICE guideline 17. Appendix M: Network meta-analysis: longacting insulin. London: National Clinical Guideline Centre; 2015.

(33) Curtis L. Unit costs of health and social care 2013. Canterbury: Personal Social Services Research Unit, University of Kent, 2013.

(34) MIMS. 2014 [cited 2013 Dec 12];Available from: URL: http://www.mims.co.uk/

(35) Joint Formulary Committee. British National Formulary (BNF) (67th ed.). London: British Medical Association and The Royal Pharmaceutical Society of Great Britain, 2014.

(36) Health and Social Care Information Centre. Prescription cost analysis - England, 2012 [NS]. 2013 [cited 2014 Jan 6];

(37) NHS Business Services Authority. NHS Electronic Drug Tariff: December 2013. 2013 [cited 2013 Dec 12];Available from: URL: http://www.ppa.org.uk/edt/December_2013/mindex.htm

(38) Currie CJ, Morgan CL, Poole CD, et al. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin 2006 Aug;22(8):1523-34.

(39) Hammer M, Lammert M, Mejias SM, et al. Costs of managing severe hypoglycaemia in three European countries. J Med Econ 2009;12(4):281-90.

(40) IMS CORE Diabetes Model Research Team, IMS Health Economics and Outcomes Research. IMS CORE diabetes model: 2011 update (version 8.0). London: IMS Health; 2014.

(41) Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the Economic Evaluation of Health Care Programmes (4th ed.) Oxford University Press, 2015.

(42) Palmer AJ, Roze S, Valentine WJ, et al. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for Type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Curr Med Res Opin 2004;20(11):1729-46.

(43) Palmer AJ, Valentine WJ, Ray JA, et al. An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1 diabetes in the UK. Curr Med Res Opin 2007;23(4):895-901.

(44) Valentine WJ, Palmer AJ, Nicklasson L, et al. Improving life expectancy and decreasing the incidence of complications associated with type 2 diabetes: a modelling study of HbA1c targets. Int J Clin Pract 2006 Sep;60(9):1138-45.

(45) Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technology Assessment 2004;8(45):iii-41.

(46) McEwan P, Poole CD, Tetlow T, et al. Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. Curr Med Res Opin 2007;23(Suppl.1):S7-S19.

(47) Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. Pharmacoeconomics 2007;25(3):253-66.

(48) Pfohl M, Schadlich PK, Dippel FW, Koltermann KC. Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. J Med Econ 2012;15(Suppl.2):14-27.

(49) The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. Diabetes 1996 Oct;45(10):1289-98.