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Cost-effectiveness Analysis of Insulin Detemir Compared to Neutral Protamine Hagedorn (NPH) in Patients with Type 1 and Type 2 Diabetes Mellitus in Portugal

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Abstract

Objectives: To estimate the short-term (1 year) cost-effectiveness of Insulin Detemir (IDet) compared with Neutral Protamine Hagedorn (NPH) insulin for Type 1 (T1DM) and Type 2 Diabetes Mellitus (T2DM) in Portugal.

Methods: A short-term cost-effectiveness model was adapted to the Portuguese National Health System (NHS), to estimate the Incremental Cost-Effectiveness Ratio (ICER) of IDet vs. NPH in terms of euros per quality-adjusted life years (€/QALY) gained. Non-severe hypoglycemia (NSH) rate for both diabetes types, and weight change, only for T2DM, were the clinical benefit variables. Three scenarios were estimated in which NPH was assigned three different values corresponding to a cohort of recent insulinization and a cohort of long-run insulinization from the UK Hypoglycemia Study and from a Spanish observational study. For all scenarios, the hypoglycemia Rate Ratio (RR) for T1DM was based on the CADTH Technology Report while for T2DM it was based on the head-to-head NCT00104182 randomized clinical trial. For T2DM, weight gain was also included in the model, based on the same RCT. Disutility values to calculate quality-adjusted life years (QALYs) were associated to NSH events and to BMI unit gain. Costs (Euros 2014), estimated from the perspective of the Portuguese NHS, included only insulin treatment and mild hypoglycemia management.

Results: For the three scenarios a range of 0.025 – 0.076 QALYs for T1DM and 0.014 – 0.051 QALYs for T2DM were gained for IDet vs. NPH due to NSH and weight gain avoidance, in return of an incremental cost of €159.38 - €248.98 for T1DM and €209.66 – €274.44 for T2DM. This resulted in IDet vs. NPH ICER ranging between €2,096.23 and €9,936.98/QALY for T1DM and €4,145.75 and €19,999.87/QALY for T2DM.

Conclusions: IDet appears as a cost-effective alternative to NPH in Portugal for T1DM and T2DM in all considered scenarios due to lower hypoglycemic rate and less weight gain.

Keywords: Insulin detemir; Neutral Protamine Hagedorn (NPH); Diabetes; Incremental Cost-Effectiveness Ratio (ICER); Quality-Adjusted Life Years (QALY); Hypoglycemic rate; Weight gain

Introduction

Diabetes mellitus (DM) is a group of heterogeneous disorders with the common features of hyperglycemia and glucose intolerance, due to insulin deficiency (type 1; T1DM), impaired effectiveness of insulin action (type 2; T2DM) or both. DM prevalence was 12.9% in the Portuguese population in 2012 [1], with 90% of cases being of T2DM [2]. All T1DM patients are treated with exogenous insulin; however, only T2DM patients who fail to achieve adequate glycemic control by other measures (exercise, diet, and/or other antidiabetic agents) will receive insulin [3].

Initial basal therapy may include either intermediate-acting (Neutral Protamine Hagedorn [NPH]) or long-acting (Insulin glargine or Detemir [IDet]) insulin formulations, which mimic more accurately the physiological profile of endogenous insulin [4]. However, insulin therapy is frequently associated with hypoglycemic episodes [5], which imply a significant economic and social impact [6].

Severe Hypoglycemia (SH) requires the assistance from another person, sometimes a medical professional or even hospitalization [7], while patients can manage Non-Severe Hypoglycemia (NSH) by themselves. Although NSHs are easier to manage, they are more frequent than severe events and represent a major management problem in diabetes patients [8]. NSH and SH are associated with direct healthcare costs and indirect costs due to the loss of productivity and work absences [7,9,10].

Weight gain is also commonly associated with insulin therapy, especially among patients with T2DM [11], and is linked to increased risk of cardiovascular morbidity and mortality [12].

Insulin analogs, such as IDet, cause fewer hypoglycemic events and less weight gain, compared to human insulins (NPH), leading to improved clinical outcomes and better health-related quality of life [13,14].

The aim of this study was to estimate the short-term cost-

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effectiveness of IDet compared with NPH insulin when initiating insulin treatment in patients with T1DM and T2DM in Portugal.

Methods

Cost-effectiveness model and patients

A cost-effectiveness model was developed using Excel 2007 (Microsoft Ltd, Redmond, WA, USA). The structure of the model is based on two Scandinavian studies: Valentine et al. (T1DM) and Ridderstråle et al. (T2DM) [15,16].

The population consisted in two hypothetical cohorts of patients with either T1DM or T2DM starting insulin treatment. The number of individuals in the cohort is irrelevant to the result as cost and clinical outcomes are expressed as average yearly costs and rates of event per patient.

One cohort of patients was treated with IDet and the other with NPH, the daily dose was assumed to be 40 IU/day, which is the Defined Daily Dose (DDD) indicated by the World Health Organization [17].

The time horizon considered was one year and the Portuguese National Health System (NHS) perspective was used, respecting the national pharmacoeconomic evaluation guideline.

Clinical data inputs

According to clinical trials, there is no significant difference in the HbA1c control and severe hypoglycemia rate between the two types of insulin treatment [13,16,18]. Therefore, the ratio of NSH, for both T1DM and T2DM patients, and weight change from baseline, only for T2DM patients, were the efficacy outcomes of choice.

Hypoglycemia rate

Three scenarios were estimated in which the NPH arm was assigned three different hypoglycemia rates.

Two scenarios were defined based on data from an observational prospective study, the UK Hypoglycemia Study, [18] conducted in six UK secondary care diabetes centers over 9-12 months which was the main source of the NSH rate for both T1DM and T2DM patients treated with NPH. A total of 383 patients aged 17-75 years were asked to self-report all NSH (self-treated) and SH episodes (requiring medical assistance), recording their glucose levels during reported episodes.

More recently, an observational cross-sectional stud carried out in Spain [19], was chosen to estimate the third scenario, describing the frequency of self-reported NSH and SH events in people with T1DM and T2DM. A total of 630 individuals [n=294 (47%) with T1DM and n=336 (53%) T2DM] were enrolled to fill out a questionnaire survey of which 506 completed the 4 questionnaires of the study.

Table 1 presents the NSH rates selected from the two studies described above [18,19], which were assumed to correspond to NSH and to be attributable to NPH treatment in T1DM and T2DM, respectively.

Hypoglycemia rate ratio

Lacking a robust source for the NSH IDet/NPH ratio, the IDet/NPH Rate Ratio (RR) for overall hypoglycemic events in T1DM patients was extracted from a systematic review and meta-analysis study carried out by the Canadian Agency for Drugs and Technologies in Health (CADTH) [14] and aimed to evaluate the clinical efficacy and safety of the long-acting insulin analogues compared with intermediate- and long-acting unmodified human insulins and Oral Antidiabetic Drugs (OADs) for the treatment of type 1, type 2, and gestational diabetes.

The NSH IDet/NPH RR was estimated at 0.52 (0.44-0.61) for T2DM patients [16], on the basis of a multicenter, randomized, open-label, 3-arm (morning or evening IDet vs. evening NPH), parallel-group clinical trial [13], conducted in 91 centers across Europe and in United States during 20-weeks with the enrollment of a total of 504 patients.

Finally, applying the NSH IDet/NPH for T1DM 0.84 (0.74-0.97) [14] and T2DM 0.52 (0.44-0.61) [13] patients to the different NSH rates attributed to the NPH arm in each scenario, the NSH rate in the IDet arm was estimated as shown in Table 1.

Weight

The same RCT [13] used for the NSH IDet/NPH RR reported an increase in body weight following insulin initiation in both evening IDet and NPH insulin groups (0.7 kg vs. 1.6 kg, respectively) with respect to the baseline, the mean difference being = 0.91 kg ($p < 0.005$) in T2DM patients.

Costs

Only pharmacy and NSH management costs were included in the model. Costs were computed from the Portuguese NHS perspective and expressed in euros of the year 2014 (Table 2). NSH management costs correspond to the cost of 5.6 extra glucose test strips [10,16] with a unit cost of 0.3110€ [20] and a visit to general practitioner for the 25% of the cohort by their unit cost (31€ [21]), as reported Brod et al. [10]. Total cost rises to 9.4916€ (0.3110*5.6 + 31*0.25).

Utilities

The utility value for symptomatic NSH for T1DM and T2DM patients was -0.0054, which was calculated by averaging the utility

Source	Cohort	NPH NSH rate (NSH/patient-year) [95% CI]	Overall hypoglycemia [14] IDet/NPH rate ratio	Approximate NSH IDet rate (NSH/patientyear)
T1DM				
UK Hypoglycemia Study Group [18]	Insulin < 5 years	35.5 [22.8-48.2]	0.84	35.5*0.84=29.82
UK Hypoglycemia Study Group [18]	Insulin > 15 years	29.0 [16.4-41.8]	0.84	29.0*0.84=24.36
Orozco-Beltrán et al. [19]	T1DM	88.0	0.84	88.0*0.84=73.92
T2DM				
UK Hypoglycemia Study Group [18]	Insulin < 2 years	4.08 [2.4-5.8]	0.52	4.08*0.52=2.12
UK Hypoglycemia Study Group [18]	Insuilin > 5 years	10.2 [5.4-15.0]	0.52	10.2*0.52=5.30
Orozco-Beltrán et al. [19]	T2DM – Basal Only Therapy (T2BOT)	18.3	0.52	18.3*0.52=9.52

Table 1: NSH rates assigned to NPH cohort and estimated NSH rates for IDet cohort in T1DM and T2DM patients.

Drug	Unit cost (€/IU)	Source	DDD	Source	Treatment cost/day
IDet (Levemir® Novo Nordisk)	0.0423	20	40 IU/day	17	0.0423€/IU*40IU/day=1.690€
Insulin NPH (Insulatard® Penfill® Novo Nordisk)	0.0222	20	40 IU/day	17	0.0222€/IU*40IU/day=0.888€

Table 2: Daily drug costs from the perspective of the Portuguese NHS.

		QALYs	ΔQALYs	Annual cost (€)			ΔCosts (€)	ICER (€/QALY)
				Pharmacy	NSH management	Total		
T1DM								
NSH rate $_{NPH}$=29.0	**IDet**	0.868	**0.025**	617	231.22	848.22	**248.98**	**9,936.98**
	NPH insulin	0.843		323.97	275.26	599.23		
NSH rate $_{NPH}$=35.5	**IDet**	0.839	**0.031**	617	283.04	900.05	**239.09**	**7,795.70**
	NPH insulin	0.808		323.97	336.95	660.96		
NSH rate $_{NPH}$=88.0	**IDet**	0.601	**0.076**	617	701.62	1,318.62	**159.38**	**2,096.23**
	NPH insulin	0.525		323.97	835.26	1,159.23		
T2DM								
NSH rate $_{NPH}$=4.08	**IDet**	0.986	**0.014**	617	20.14	637.14	**274.44**	**19,999.87**
	NPH insulin	0.972		323.97	38.73	362.7		
NSH rate $_{NPH}$=10.2	**IDet**	0.969	**0.03**	617	50.35	667.35	**246.56**	**8,334.80**
	NPH insulin	0.939		323.97	96.82	420.79		
NSH rate $_{NPH}$=18.3	**IDet**	0.946	**0.051**	617	90.33	707.33	**209.66**	**4,145.75**
	NPH insulin	0.996		323.97	173.7	497.67		

Table 3: Base-case cost-effectiveness results for T1DM and T2DM patients in Portugal with different NSH rates for NPH arm.

associated to nocturnal and diurnal episodes [22]. The BMI increment was estimated in -0.0100 per BMI unit increase [23] for T2DM patients (considering the mean height of Spanish population of 1.7 m [24]: ΔBMI=Δweight*0.346).

Sensitivity analysis

To assess model uncertainty a One-Way Sensitivity Analysis (OWSA) and a Probabilistic Sensitivity Analysis (PSA) according to suitable probability distributions (log-normal for hypoglycemia rates and rate ratios, normal for the weight changes, beta for disutilities, and Gamma for hypoglycemia costs and insulin doses) were performed.

Results

Due to lower NSH rates, IDet treatment yields an improvement of 0.025-0.076 QALYs compared to NPH, in the base-case scenario, at an incremental cost of €159 - €249 per patient and year, in T1DM. Therefore, the Incremental Cost-Effectiveness Ratio (ICER) for IDet vs. NPH insulin in T1DM was estimated at €2,096/QALY - €9,937/QALY in Portugal, depending on the considered hypoglycemia rate (Table 3).

For T2DM patients, IDet was associated to less NSH episodes and less weight gain compared to NPH insulin, resulting in a 0.014 - 0.051 QALY gain in the base-case, in return of an incremental cost of €210 - €274 for the Portuguese NHS. Therefore, the IDet vs. NPH insulin ICER was estimated at €4,146 - €20,000/QALY, in relation to the considered hypoglycemia rate (Table 3).

OWSA results are shown in Figure 1 for T1DM and T2DM, respectively. The variable that has the highest impact on the ICER for T1DM is IDet/NPH hypoglycemia RR, with ICER values of €4,121-49,194/QALY, when it varies between 0.74 and 0.97. The second variable with the highest impact is the cost of IDet treatment, which makes ICER decrease to €3,773/QALY when decreased by 20%, and increase up to €11,819/QALY, when increased by 20% (Figure 1A). In T2DM, the variable with the highest impact on ICER is IDet daily cost. When increasing or decreasing it by 20%, the ICER varies between €12,354/QALY and €29,035/QALY. NPH cost variation (± 20%) is the second most sensitive variable, yielding ICERs of €24,626-16,764/QALY (Figure 1B).

Cost-effectiveness acceptability curves are shown in Figure 2 for T1DM and T2DM, respectively, presenting a probability of cost-effectiveness at a €24,163/QALY threshold of about 87% and 67% in T1DM and T2DM, respectively.

Discussion

This short-term cost-effectiveness analysis is based on previously published economical evaluations for Scandinavian countries [15,16] and relies on statistically significant efficacy differences between IDet and NPH.

There are no officially established acceptability thresholds for ICERs in Portugal; however, according to WHO, a health product is highly cost-effective if its ICER stays beneath the average GDP per capita, being for Portugal (WHO Euro A region) $30,439 (year 2005, currently €24,163) [25,26]. This evaluation showed that IDet vs. NPH insulin is associated to an ICER that stays below this threshold for considered scenarios.

OWSA shows that model results are robust, all ICERs remain below the cost-effectiveness acceptability threshold. The one exception is attributing an IDet/NPH hypoglycemia RR close to 1 (0.97) in T1DM [14], which would imply that IDet does not provide any relevant incremental health benefit on hypoglycemia rate vs. NPH. Another sensitive variable, in both diabetes types, is the treatment cost. PSA simulations reveal a probability of cost-effectiveness at a €24,163/QALY threshold of about 87% and 67% in T1DM and T2DM, respectively.

The results of this evaluation must be interpreted in the context of its limitations. First, only short-term is considered. In fact, this might underestimate the real clinical benefits of IDet with respect to NPH, as hypoglycemia rate is expected to increase with treatment duration [16].

To address the importance of the absolute rate of NSH in the NPH treatment arm in the cost-effectiveness of IDet vs. NPH, three scenarios were assessed in the base-case analysis. The first two scenarios, use NSH rates coming from the UK Hypoglycemia Study that is a reference observational study for hypoglycemia in diabetic patients. Two NSH rates have been selected: one corresponding to patients that recently

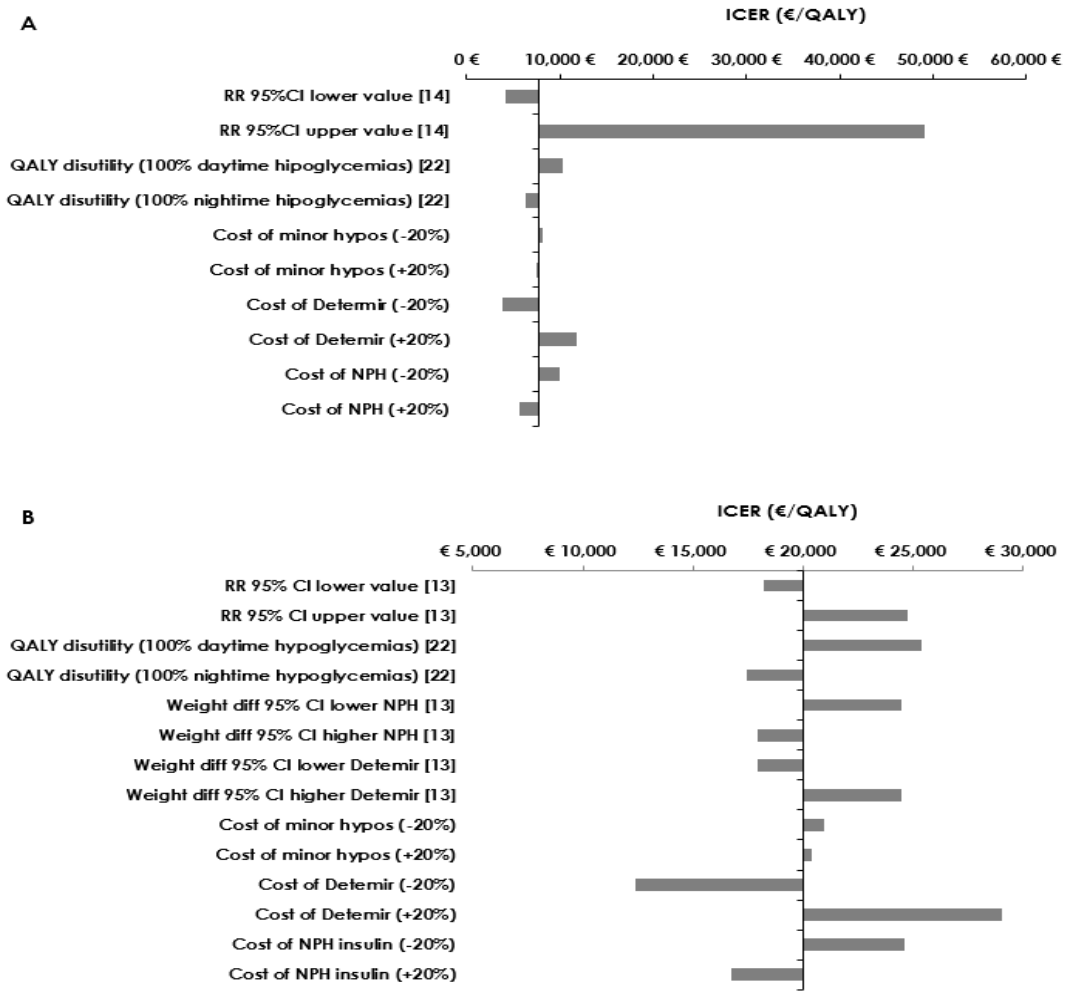

Figure 1: One-way sensitivity analyses for insulin IDet vs. NPH for A) T1DM patients (for NPH NSH rate=35.5) and B) T2DM patients (for NPH NSH rate=4.08) (CI=confidence interval).

began insulin treatment, and one corresponding to patients with long run insulin treatment [18]. The third scenario is based on NSH rates from a recently published observational study performed in Spain [19], which should be considered as the closest to the "real world" situation of the Portuguese NHS in that population characteristics and the NSH structure are more similar between these two Iberian countries than to UK. The three scenarios all provide cost-effective results. It should be considered, however, that NSH rates of these studies were assumed to correspond to treatment with NPH, although insulin type information was not available and most probably the study groups were receiving different insulin types. However, this is a conservative assumption, in that, NPH is known to be associated to higher hypoglycemia rates than more modern insulin analogs [27].

As the hypoglycemia rate was an overall value (no distinction between nocturnal and diurnal NSH events), the utilities associated to diurnal and nocturnal events [10] were averaged to obtain a unique value. However, this simplification was tested in the OWSA by assuming 100% nocturnal or 100% diurnal events and attributing the corresponding utility values. In both ICER estimations, IDet resulted cost-effective with respect to NPH.

Additionally, the use of an overall hypoglycemia RR for IDet vs. NPH, instead of a specific RR for NSH episodes, due to the lack of a robust source, may be considered a limitation of the model. However, the approximated values that are maintained from the original models [15,16] give conservative estimations of the NSH RR, as already discussed by Valentine et al. in their paper [15], and offer the advantage of integrating data from a very controlled setting (RCTs [13,14]), with a setting that is closer to the "real world" data (observational study [18,19]), as explained by Ridderstrale et al. [16].

Finally, the WHO DDD for insulin has been used [17], which is not a "real world" dose for diabetic patients; however, robust data in this sense are not available, due to the dosing variability in the clinical practice. Considering all the exposed assumptions, this may be considered a conservative estimation.

Recent cost-effectiveness evaluations of IDet vs. NPH or any other insulins were not publicly available in Portugal. However, two studies assessing long-term cost-effectiveness of OADs in T2DM patients have been published. Viriato et al. [28] adapted an UK-based discrete event simulation model to Portugal, estimating for metformin plus vildagliptin vs. metformin plus sulphonylurea an ICER of €9,072/QALY over the patient's lifetime. Schwartz et al. [29] have also adapted an UK-based discrete event simulation model to six European countries,

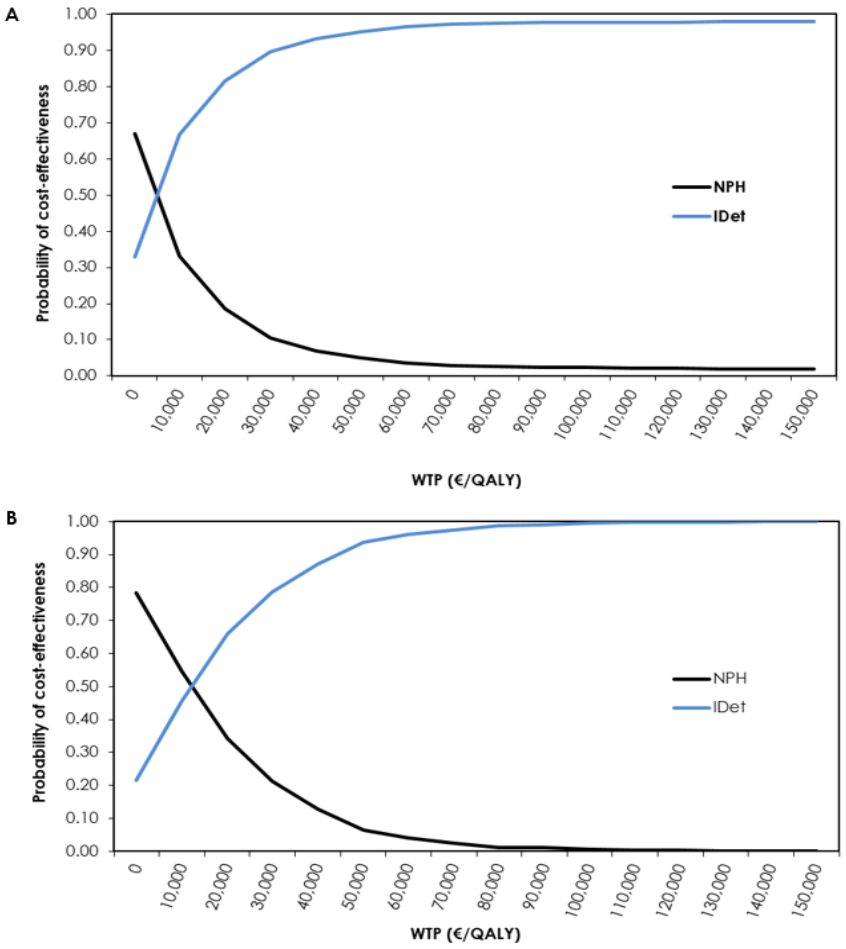

Figure 2: Cost-effectiveness acceptability curve for IDet vs. NPH in A) T1DM patients (for NPH NSH rate=35.5) and B) T2DM (for NPH NSH rate=4.08).

including Austria, Finland, Portugal, Scotland (United Kingdom), Spain and Sweden. The model evaluated the cost-effectiveness of adding either sitagliptin or sulphonylurea to metformin in patients failing to achieve HbA1c control on metformin alone. In this case, the estimated ICER for Portugal was €5,949/QALY, while the reported ICERs for the other countries fell in the range of €11,547 - €20,350 (year 2007) over the patient's lifetime.

On the other hand, short-term cost-effectiveness analyses for IDet vs. NPH are available for Scandinavian countries estimating ICERs in the range of €12,216 – €16,568/QALY (year 2010) for T1DM [15] and €21,768 – €28,349/QALY (year 2012) for T2DM [16] over a 1 year period.

Given the scarcity of cost-effectiveness estimation for antidiabetic treatments in Portugal, this IDet vs. NPH short-term evaluation can support healthcare decision makers with immediate budget considerations.

In conclusion, this analysis shows in a direct manner that IDet can be considered cost-effective with respect to NPH insulin in a Portuguese setting for the treatment of both T1DM and T2DM patients, with ICERs that are in the line of or even smaller than those calculated for other European countries, and in the range commonly accepted for Portugal.

References

1. Diabetes Facts and Nameros (2013) Relate Annual National Observatory of Diabetes.
2. World Health Organization (1999) Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO Consultation. Part1: Diagnosis and classification of diabetes mellitus. Geneve: World Health Organization.
3. American Diabetes Association (2014) Standards of medical care in diabetes 2014. Diabetes Care 37: S14-S80.
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, et al. (2012) Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care 35: 1364–1379.
5. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, et al. (2013) Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 36: 1384-1395.
6. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, et al. (2009) Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 94: 709-728.
7. Hammer M, Lammert M, Mejías SM, Kern W, Frier BM (2009) Costs of managing severe hypoglycaemia in three European countries. J Med Econ 12: 281-290.
8. Cryer PE (2002) Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. Diabetologia 45: 937-948.
9. Williams SA, Shi L, Brenneman SK, Johnson JC, Wegner JC, et al. (2012)

The burden of hypoglycemia on healthcare utilization, costs, and quality of life among type 2 diabetes mellitus patients. J Diabetes Complications 26: 399-406.

10. Brod M, Wolden M, Christensen T, Bushnell DM (2013) A nine country study of the burden of non-severe nocturnal hypoglycaemic events on diabetes management and daily function. Diabetes Obes Metab 15: 546-557.
11. Pontiroli AE, Miele L, Morabito A (2011) Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. Diabetes Obes Metab 13: 1008-1019.
12. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Nunez L, et al. (2009) Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. Diabetologia 52: 65-73.
13. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, et al. (2006) Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 28: 1569-1581.
14. Canadian Agency for Drugs and Technology in Health (2010) Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta analyses of Clinical Outcomes. CADTH Technol Overv 1: e0113.
15. Valentine WJ, Jendle J, Saraheimo M, Thorsteinsson B, Pollock RF, et al. (2012) Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type 1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands. Diabet Med 29: 303-312.
16. Ridderstrale M, Jensen MM, Gjesing RP, Niskanen L (2013) Cost-effectiveness of insulin detemir compared with NPH insulin in people with type 2 diabetes in Denmark, Finland, Norway, and Sweden. J Med Econ 16: 468-478.
17. WHO (2014) ATC/DDD index.
18. UK Hypoglycaemia Study Group (2007) Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 50: 1140-1147.
19. Orozco-Beltran D, Mezquita-Raya P, de Arellano AR (2014) Self-reported frequency and impact of hypoglycemic events in Spain. Diabetes Ther 5: 155-168.
20. Infarmed (2014) Autoridade Nacional do Medicamento e Productos de Salude I.P.
21. https://dre.pt/application/dir/pdf1sdip/2014/01/02000/0059700703.pdf
22. Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T (2014) Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin - from the UK health care cost perspective. Diabetes Obes Metab 16: 366-375.
23. Lee AJ, Morgan CL, Morrissey M, Wittrup-Jensen KU, Kennedy-Martin T, et al. (2005) Evaluation of the association between the EQ-5D (health-related utility) and body mass index (obesity) in hospital-treated people with Type 1 diabetes, Type 2 diabetes and with no diagnosed diabetes. Diabet Med 22: 1482-1486.
24. National Institute of Statistics (2016) Mean height of the population by country, sex, year, and age.
25. Kaur P, Kwatra G, Kaur R, Pandian JD (2014) Cost of stroke in low and middle income countries: a systematic review. Int J Stroke 9: 678-682.
26. WHO-CHOICE (2014)
27. Monami M, Marchionni N, Mannucci E (2008) Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 81: 184-189.
28. Viriato D, Calado F, Gruenberger JB, Ong SH, Carvalho D, et al. (2014) Cost-effectiveness of metformin plus vildagliptin compared with metformin plus sulphonylurea for the treatment of patients with type 2 diabetes mellitus: a Portuguese healthcare system perspective. J Med Econ 17: 499-507.
29. Schwarz B, Gouveia M, Chen J, Nocea G, Jameson K, et al. (2008) Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and haemoglobin A1c above target on metformin monotherapy. Diabetes Obes Metab 1: 43-55.