Cost-Effectiveness Analysis of Exenatide versus GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus

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Background

- Type 2 diabetes mellitus (T2DM) in an endocrine and metabolic disorder that manifests when the body is unable to effectively use insulin to regulate blood glucosa level[1].
- Currently, the incorporation of glucagon-like peptide-1 (GLP-1) receptor agonists have expanded the treatment options for T2DM. These new therapeutic agents to initial therapy with metformine has been becoming more relevant due to reduction HbA_{1c} levels, without the adverse effects of hypoglycaemia or the weight gain of other oral antidiabetics drugs[2].

Objective

To assess the cost-effectiveness of exenatide compared to other GLP-1 receptor agonists available in Spain, in T2DM patients not adequately-controlled on metformin alone.

Methods

- A stochastic model of discrete events (*Cardiff Diabetes Model*)[3], was adapted to the Spanish setting, to estimate the quality-adjusted life years (QALYs) gained and total costs of assessed drugs over a time horizon of 40 years.
- The patient's evolution was biannually modelled based on UKPDS68 equations[4] simulating the disease evolution considering the T2DM-related micro- and macro-vascular complications (ischemic heart disease, myocardial infarction, stroke, congestive heart failure, amputation, blindness and end-stage renal disease), hypoglycemia, nausea, body-mass-index (BMI) changes and treatment discontinuation due to adverse events (AE).
- Initial demographic and clinical characteristics for T2DM assessed patients derived from literature[5-10] (Table 1).
- Efficiency of exenatide 2 mg/weekly (EQW2) vs. dulaglutide 1.5 mg/weekly (DULA 1.5), vs. liraglutide 1.2 mg/daily (LIRA 1.2), vs. liraglutide 1.8 mg/daily (LIRA 1.8) and vs. lixisenatide 20 µg/daily (LIXI 20) was determined. All these therapies combined with metformine 2 g/daily.

Table 1. Demographic and clinic characteristics

Demographic characteristics	Value
Age (years)	67.70
Proportion female (%)	47.1%
Duration of type 2 diabetes mellitus (years)	10.07
Height (meters)/ Weight (kg)	1.67 m/73.50 kg
Proportion smokers (%)	12.10%
Clinic characteristics	
Basal HbA_{1c} level	7.28
Total cholesterol/High-density lipoprotein cholesterol (mg/dl)	200.60/42.30
Systolic blood pressure (mm Hg)	125.40

- The efficacy of alternatives were obtained from a indirect comparison performed in a network meta-analysis[11](Table 2).
- Baseline utility value (0.80) derived from PANORAMA study[6]. Utility decrements associated to micro- and macro-vascular complications occurrence[4,12], hypoglycemia episodes[13] and BMI changes[14] were applied (Table 3).
- Treatment discontinuation due to AE, or poor control of diabetes (HbA_{1c} >7,5%) involved switch to 2nd with basal insulin (40 IU/daily) or 3rd line with basal insulin and bolus insulin (20 IU/daily).
- The National Health System perspective was considered, including direct costs (€,2018): drug-acquisition costs (Table 2), severe hypoglycemia, BMI increase, micro- and macro-vascular complications, nauseas and treatment discontinuation due to AE (Table 3).
- An annual discount rate of 3% was applied to costs and health outcomes[15].
- Deterministic and probabilistic sensitivity analyses (SA) were performed.

Table 2. Therapeutic alternatives: efficacy and costs

	MET 2	EQW 2	DULA 1.5	LIRA 1.2	LIRA 1.8	LIXI 20	NPH	
ΔHbA_{1c} (%)	—	-1.34	-1.34	-0.96	-1.28	-0.75	-0.54	
ΔWeight (kg)	—	-2.04	-2.38	-2.72	-3.09	-1.84	-1.703	
Discontinuation of treatment	—	0.063	0.140	0.120	0.130	0.030	—	
Nausea	—	0.240	0.520	0.440	0.490	0.310	—	
Symptomatic hypoglycemia	—	—	—	—	—	—	10.922	
Severe hypoglycemia	—	—	—	—	—	—	0.02	
	MET 2	EQW 2	DULA 1,5	LIRA 1,2	LIRA 1,8	LIXI 20	Ins. basal	Ins. en bolus
Annual drug cost*	€33.35	€1,217.59	€1,821.42	€1,555.97	€2,333.95	€1,503.13	€0.019 kg/daily	€0.008 kg/daily

NPH: Neutral-Protamina-Hagedorn. *Retail-prices plus VAT[16] with mandatory deduction[17]

Table 3. Utility decrement and costs related to complications

	Utility decrement	First-year cost		Maintenance cost per year
		Fatal events	Non-fatal event	
Ischemic heart disease	- 0.090	—	€2,335	€887
Myocardial infarction	- 0.055	€4,755	€5,132	€887
Congestive heart failure	- 0.108	€4,755	€3,451	€3,662
Stroke	- 0.164	€4,755	€6,532	€2,551
Amputation	- 0.280	€3,782	€11,605	€1,702
Blindness	- 0.074	—	€1,932	€829
End stage renal disease	- 0.175	—	€31,451	€31,451
BMI – per unit increase	- 0.0472			
BMI – per unit decrease	+ 0.0171			
Symptomatic hypoglycemia	- 0.0142	**Episode cost**		
Severe hypoglycemia	- 0.047	€1,154		
Nausea	—	€59.77		
Discontinuation of treatment	—	€59.77		

Results

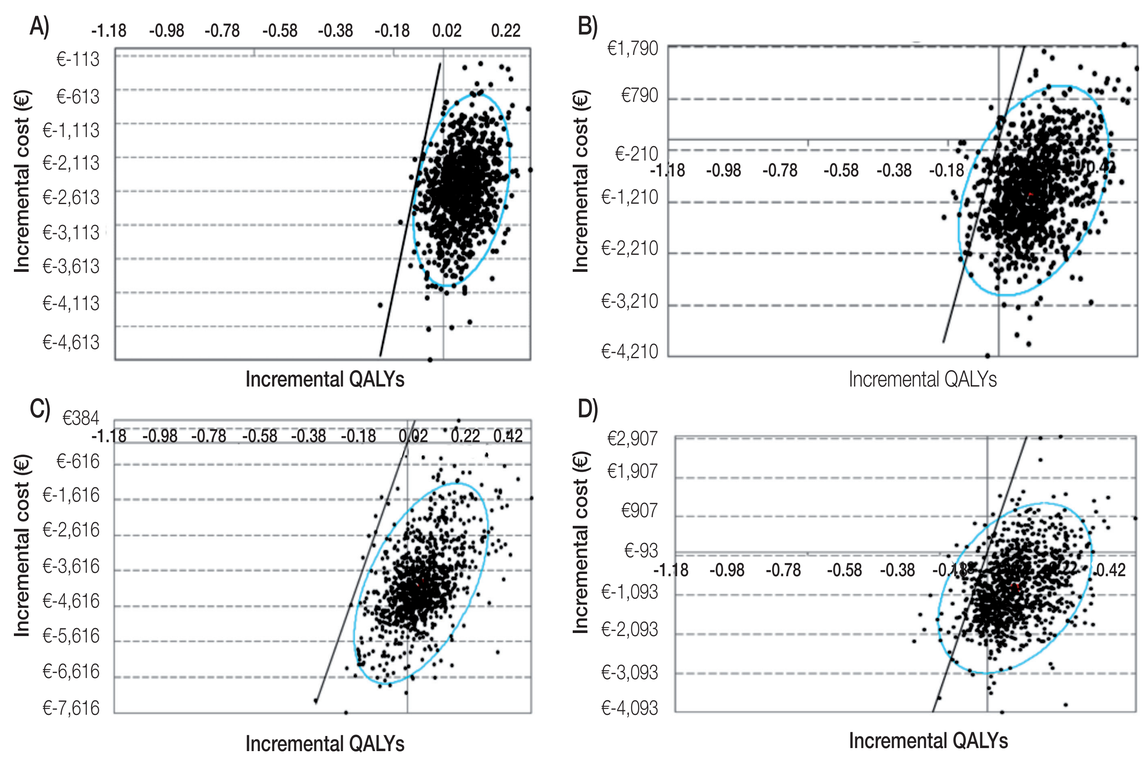
- EQW2 resulted in greater QALYs (8.26) than DULA 1.5 (8.19 QALYs), LIRA 1.2 (8.10 QALYs), LIRA 1.8 (8.20 QALYs) and LIXI 20 (8.13 QALYs) (Table 4).
- Total costs/patient resulted €20,423.27 (EQW2), €22,611.94 (DULA 1.5), €21,065.97 (LIRA 1.2), €24,865.69 (LIRA 1.8) and €21,334.58 (LIXI 20) (Table 4).
- EQW2 was a dominant strategy (more effective and less costly) versus all the other GLP-1 (Table 4).

Table 4. Base case results

	DULA 1.5	LIRA 1.2	LIRA 1.8	LIXI 20
Incremental QALYs (EQW2 vs.)	0.07	0.15	0.06	0.12
Incremental costs (EQW2 vs.)	€ -2,189	€ -643	€ -4,442	€ -911
ICER (EQW2 vs.)	Dominant	Dominant	Dominant	Dominant

- Deterministic SA confirmed the model robustness.
- For a willingness-to-pay threshold of €20,000/QALY gained[18], EQW2 resulted a cost-effective option compared to the other GLP-1, in 95-99% of the 1,000 MonteCarlo iterations of the probabilistic SA (Figure 1).

Figure 1. Probabilistic Sensitivity Analyses



A) EQW2 vs DULA 1.5; B) EQW2 vs LIRA 1.2; C) EQW2 vs LIRA 1.8; D) EQW2 vs LIXI 20

Conclusions

- Exenatide 2 mg/weekly would be a dominant alternative (more effective and less costly) versus the other GLP-1 for the treatment of T2DM patients not adequately-controlled on metformin alone.

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