Systematic review of economic evaluations of dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus.

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Background

- Type 2 diabetes mellitus (T2DM) is a chronic disease, requiring continuous medical care and therapeutic actions to prevent complications and to improve health outcomes of patients[1], with a high prevalence and a relevant economic impact. In Spain, the total direct annual cost of diabetes mellitus (DM) represents an 8.2% of the total Spanish health expenditure (the 90% corresponds to T2DM). Antidiabetic drugs costs imply a 15% of the total cost, and the cost of complications is around 37% of the total[2].
- The increase use of newer and more expensive drugs such as glucagon-like peptide-1 (GLP-1) analogues or dipeptidyl peptidase-4 (DPP-4) inhibitors, with the increasing incidence of T2DM, has a significant economic impact for healthcare systems. Therefore, it is necessary to identify if these agents offer significant advantages over older therapies[3].

Objective

- To synthesize and analyze the available information on the therapeutic value of DPP-4 inhibitors for the treatment of T2DM considering their efficiency or cost-effectiveness.

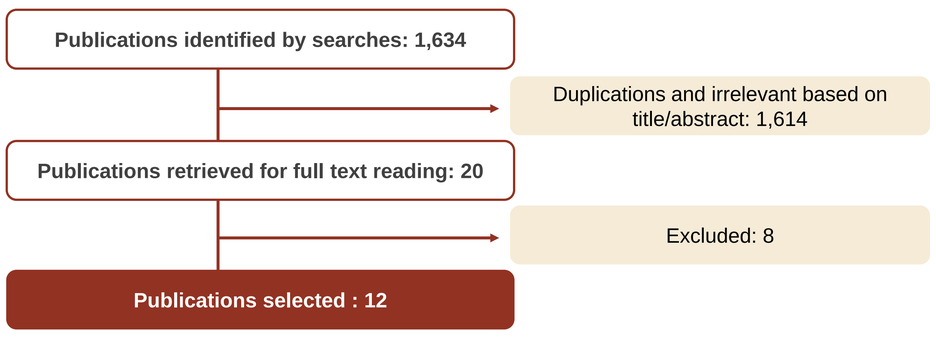
Materials and methods

- A systematic literature search in Spanish (MEDES, IBECS) and international (MedLine/PubMed, Cochrane Library, ISI WOK, SCOPUS) databases was performed.
- Eligible studies (published in English or Spanish until June 2013) were economic evaluations comparing costs and clinical benefits of two alternatives for T2DM treatment including DPP-4 inhibitors. Studies providing data concerning costs and/or disease burden were excluded.

Results

- Of 1,634 publications initially identified, a total of 12 publications were selected for reviewing (Figure 1) .

Figure 1. Results of systematic review



- Characteristics of selected publications are described in table 1. National Health System perspective was adopted in all publications. One study did not include a sensitivity analysis[4].

Table 1. Characteristics of selected publications

First author, publication year, country (OCEBM levels of evidence)	Design, time horizon	Costs, benefits and discount rate
Elgart JF, 2013[5] Argentina (2b)	• Cost-effectiveness and cost-utility: Discrete-event simulation model (Cardiff diabetes model). • 20 years.	• **Direct costs (US$, 2009):** drugs, AEs, macro- and microvascular complications. • Benefits: LYG and QALY. • Discount rate**:** 3.5% (costs and benefits).
Langer J, 2013[6] United States (3b)	• Cost-effectiveness: Cost per patient achieving a clinically relevant composite endpoint. • 1 year.	• **Direct costs (US$, 2012):** drugs. • Benefits: proportion of patients achieving a clinically relevant composite endpoint (HbA1c<7.0%, no hypoglycaemia and no gain in body weight, based on a published trial). • Discount rate: 0%.
Bergenheim K, 2012[7] United States (2b)	• Cost-utility: Discrete-event simulation model (Cardiff Long Term Cost-Utility Model). • 5 and 40 years (patient life-time).	• **Direct costs (US$, 2009):** drugs, macro- and microvascular complications. • Benefits: QALY. • Discount rate: 3% (costs and benefits).
Davies MJ, 2012[8] UK (3b)	• Cost-utility: Markov (CORE diabetes model). • Patient life-time.	• **Direct costs (£, 2008):** drugs, BGSM, macro- and microvascular complications, hypoglycemia. • Benefits: QALY. • Discount rate: 3.5% (costs and benefits).
Erhardt W, 2012[9] Germany (1b)	• Cost-effectiveness and cost-utility: Discrete-event simulation model (Cardiff Diabetes Model). • 40 years.	• **Direct costs (€, 2009):** drugs, AEs, macro- and microvascular complications. • Benefits: LYG and QALY. • Discount rate: 3.5% (costs and benefits).
Granström O, 2012[10] Sweden (2b)	• Cost-effectiveness and cost-utility: Discrete-event simulation model. • Patient life-time.	• **Direct costs (SEK, 2008):** drugs, BGSM, macro- and microvascular complications, hypoglycemia. • Benefits: LYG and QALY. • Discount rate**:** 3% (costs and benefits).
Guillermin AL, 2012[11] United States (3b)	• Cost-effectiveness and cost-utility: Markov model (CORE diabetes model). • 35 years.	• **Direct costs (US$, 2010):** macro- and microvascular complications, hypoglycemia. Drug costs were excluded. • Benefits: LYG and QALY. • Discount rate: 3% (costs and benefits).
Lee WC, 2012[12] United States (2b)	• Cost-effectiveness and cost-utility: Markov model (CORE diabetes model. • 35 years.	• **Direct costs (US$, 2011):** drugs, BGSM, macro- and microvascular complications, hypoglycemia. • Benefits: LYG and QALY. • Discount rate: 3% (costs and benefits).
Nita ME, 2012[13] Brazil (1b)	• Cost-effectiveness and cost-utility: Discrete-event simulation model. • Patient life-time.	• **Direct costs (R$, year not specified) in cost-effectiveness:** drugs, AEs (hypoglycemia) and macro- and microvascular complications. • Benefits: QALY. • Discount rate: 5% (costs and benefits).
Klarenbach S, 2011[14] Canada (1b)	• Cost-utility: Discrete-event simulation model (UKPDS). • Patient life-time.	• **Direct costs ($, 2009):** drugs, macro- and microvascular complications. • Benefits: QALY. • Discount rate: 5% (costs and benefits).
McEwan P, 2010[4] UK (4)	• Cost-utility: Discrete-event simulation model (Cardiff Diabetes Model). • 100 years (patient life-time).	• **Direct costs (£, 2008):** drugs, macro- and microvascular complications. • Benefits: QALY. • Discount rate: 6% at costs and 1.5% at benefits.
Schwarz B, 2008[15] Austria, Finland, Portugal, UK, Spain y Sweden (3b)	• Cost-utility: Discrete-event simulation model (UKPDS). • Patient life-time.	• **Direct costs (€, 2007):** drugs, AEs (hypoglycaemia, weight), macro- and microvascular complications. • Benefits: QALY. • Discount rate: 3% (costs and benefits) in Sweden/Austria, 3.5% in UK, 5% in Portugal/Finland, and 6% in Spain.

AEs: adverse events; BGSM: blood glucose self-monitoring; LYG: life years gained; OCEBM: Oxford Centre for Evidence Based Medicine; QALY: quality adjusted life years; UK: United Kingdom.

- Key cost-effectiveness results for each study are included in figure 2.

Figure 2. Cost-effectiveness result of each study

	Comparator	*Intervention*	*Results*	*Threshold*
Elgart JF, 2013 Argentina	MET + SU (dose not specified)	MET + Saxagliptin (dose not specified)	ICUR 7,374 $/QALY ICER 20,490 $/LYG	Cost-effective
Langer J, 2013 United States	Liraglutide (1.2 mg) + MET (1,500 mg)		US$ 10,335	NA (cost per patient achieving an endpoint)
	Liraglutide (1.8 mg) + MET (1,500 mg)		US$ 11,755	
	Sitagliptin (100 mg) + MET (1,500 mg)		US$ 16,858	
Bergenheim K, 2012 United States	MET + Glipizide (dose not specified)	MET + Saxagliptin (dose not specified)	ICUR 1,052 $/QALY	Cost-effective
Davies MJ, 2012 United Kingdom	SU (4 mg) + MET	Liraglutide (1.2 mg) + MET	ICUR 9,449 £/QALY	Cost-effective (20,000-30,000 £/QALY)
	SU (4 mg) + MET	Liraglutide (1.8 mg) + MET	ICUR 16,501 £/QALY	
	Sitagliptin (100 mg) + MET	Liraglutide (1.2 mg) + MET	ICUR 9,851 £/QALY	
	Sitagliptin (100 mg) + MET	Liraglutide (1.8 mg) + MET	ICUR 10,465 £/QALY	
Erhardt W, 2012 Germany	MET + Saxagliptin (dose not specified)	MET + Sulfonylurea (dose not specified)	ICUR 13,931 €/QALY ICER 241,896 €/LYG	Cost-effective (authors)
Granström O, 2012 Sweden	MET (2,000 mg) + SU (14.7 mg)	MET (2,000 mg) + Saxagliptin (5 mg)	ICUR 91,260 SEK/QALY	Cost-effective (500,000 SEK/QALY)
Guillermin AL, 2012 United States	Sitagliptin (100 mg)	Exenatide (2 mg/week)	LYG: 0.28; QALY: 0.28; Complications costs: US$ - 2,215	NA (drug cost not included)
	Pioglitazone (45 mg)	Exenatide (2 mg/week)	LYG: 0.17; QALY: 0.24; complications costs: US$ - 933	
Lee WC, 2012 United States	MET (1,000 mg) + Sitagliptin	MET (1,000 mg) + Lira (1.2 mg)	ICUR 37,234 US$/QALY	Cost-effective
	MET (1,000 mg) + Sitagliptin	MET (1,000 mg) + Lira (1.8 mg)	ICUR 25,742 US$/QALY	
Nita ME, 2012 Brazil	MET + Pioglitazone (dose not specified)	MET + Saxagliptin (dose not specified)	ICER Dominant	Cost-effective
Klarenbach S, 2011 Canada	MET	MET (2,000 mg) + SU (10 mg)	ICUR 12,757 $/QALY	Authors expressed that DPP-4 inhibitors are dominated by TZD only if it is assumed that use of TZD is not associated with an increased risk of congestive heart failure. However, evidence suggests that use of TZD is associated with an increased risk of congestive heart failure, then use of DDP-4 inhibitors and insulin is more cost-effective than TZD.
	MET (2,000 mg) + SU (10 mg)	MET (2,000 mg) + Meglitinide (4 mg)	ICUR Dominated	
	MET (2,000 mg)< + SU (10 mg)	MET (2,000 mg) + Alpha-glucosidase inhibitors (300 mg)	ICUR 939,479 $/QALY	
	MET (2,000 mg) + Alpha-glucosidase inhibitors (300 mg)	MET (2,000 mg) + TZD (30 mg)	ICUR 4,621,828 $/QALY	
	MET (2,000 mg) + TZD (30 mg)	MET (2,000 mg) + DPP-4 inhibitor (100 mg)	ICUR Dominated	
	MET (2,000 mg) + TZD (30 mg)	MET (2,000 mg) + basal insulin (0.75 U/Kg)	ICUR Dominated	
	MET (2,000 mg) + TZD (30 mg)	MET (2,000 mg) + biphasic insulin (1.50 U/Kg)	ICUR Dominated	
McEwan P, 2010 United Kingdom	MET (1st line), MET + SU (2nd), MET + SU + TZD (3rd)		609 £/QALY	NA (cost per QALY)
	MET (1st line), MET + TZD (2nd), MET + SU + TZD (3rd)		793 £/QALY	
	MET (1st line), MET+ DPP-4 inhibitor (2nd), MET + DPP-4 inhibitor + SU (3rd)		756 £/QALY	
	MET (1st line), MET+ SU (2nd), MET + SU + DPP-4 inhibitor (3rd)		611 £/QALY	
Schwarz B, 2008 Austria, Finland, Portugal, United Kingdom, Spain y Sweden	Sitagliptin + MET	SU + MET	**ICUR** 20,350 €/QALY Austria 13,737 €/QALY Finland 5,949 €/QALY Portugal 11,547 €/QALY UK 13,440 €/QALY Spain 12,219 €/QALY Sweden	Cost-effective

DPP-4: dipeptidyl peptidase; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; LYG: life year gained; OCEBM: Oxford Centre for Evidence Based Medicine; QALY: quality adjusted life year; TZD: thiazolidinedione; SU: sulfonylurea; MET: metformin. NA: not applicable.

- Results showed that T2DM therapy with DPP-4 inhibitors and metformin resulted cost-effective compared with sulfonylureas plus metformin in all the countries which were evaluated (Sweden, United Kingdom, Germany, Portugal, Austria, Finland, Spain, USA and Argentina).
- Although DPP-4 inhibitors cost was higher compared with sulfonylureas, DPP-4 inhibitors plus metformin were associated to higher clinical benefits versus sulfonylureas plus metformin in terms of decreasing hypoglycemia incidence and T2DM complications.

Conclusions

- **DPP-4 inhibitors added to metformin are a cost-effective alternative compared with sulfonylureas plus metformin in T2DM patients, mainly due to a lower hypoglycemia incidence and T2DM complications.**

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