Cost-effectiveness of vildagliptin for people with Type 2 Diabetes Mellitus in Brazil; findings and implications

Gustavo Laine Araujo de Oliveira[1], Augusto Afonso Guerra Junior[1,2], *Brian Godman[3,4], Francisco de Assis Acurcio[1,2,5]

[1]Department of Social Pharmacy, School of Pharmacy, Federal University of Minas Gerais, Belo Horizonte, Brazil. Email: gustavolaine@gmail.com; augustoguerramg@gmail.com; acurcio@ufmg.br
[2]SUS Collaborating Centre – Technology Assessment & Excellence in Health, College of Pharmacy, Federal University of Minas Gerais, Minas Gerais, Brazil
[3]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK. Email: Brian.godman@strath.ac.uk
[4]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden. Email: Brian.Godman@ki.se
[5]School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil

*Correspondence author: Brian Godman, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: Brian.godman@strath.ac.uk. Telephone: 0141 548 3825. Fax: 0141 552 2562 and Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se. Telephone: 00468 585 81068; Fax: 00468 585 81070

Abstract

Introduction: Vildagliptin is an inhibitor of the enzyme dipeptidyl peptidase 4, indicated for the treatment of type 2 diabetes mellitus, combined or not with metformin. This study aims to evaluate the cost-effectiveness of vildagliptin in the Brazilian context. Areas covered: Using MEDLINE, Cochrane Library, Lilacs and CRD, six studies were selected for the economic models. This study utilised cost data in the Brazilian health system to provide the context. Expert commentary: Type 2 diabetes mellitus is an epidemic disease and represents a challenge for all health care systems. Although guidelines clearly define first-line treatment, there are several other promising treatments. Vildagliptin is one of them, resulting in a mean lifetime increase of 0.31 years compared to metformin alone and 1.19 more life years compared to other metformin combinations. Considering observational data, life years with dual vildagliptin-containing treatments were 0.37 more compared to other dual treatments. However, its high cost versus generic metformin and its unclear safety profile weakens its subsequent cost-effectiveness. Consequently, the incorporation of vildagliptin or its combination with metformin is currently not recommended for the Brazilian Health Care System. This may change as more data becomes available.

Key words: vildagliptin, cost-effectiveness, Brazil, Type 2 diabetes, metformin

1. Introduction

Diabetes mellitus is a major public health problem. In 2014, it was estimated there were 422 million people worldwide with the disease, 8.5% of the adult population [1], although others estimated 415 million in 2015. In any event, the prevalence is envisaged to increase to 642

million by 2040 [2]. Globally, diabetes alone was estimated to kill 4.6 million people in 2013 [3]. Type 2 diabetes mellitus (T2DM) is the most prevalent of the type, affecting between 90% and 95% of patients with diabetes. Annual treatment expenditures of people living with diabetes is currently estimated at US$827 billion, representing 12% of the total worldwide expenditure on health. Approximately half of adults affected by diabetes are currently undiagnosed, and it is estimated that one person dies from this disease every six seconds [1,2].

There are many medicines available for treatment of patients with T2DM. Among these, there are insulin preparations including insulin analogues as well as oral and injectable and hypoglycemic agents. In the essential medicines lists of Brazil, there are regular and NPH insulins, in addition to oral hypoglycemic agents metformin, glibenclamide and gliclazide [4]. This alongside encouraging lifestyle changes including diet and exercise.

Antihypertensives, including renin-angiotensin inhibitors, statins and anti-platelet medicines are also prescribed concomitantly with hypoglycaemic medicines and insulin to reduce the complications of patients with T2DM, which include cardiovascular complications and nephropathy [5–7]. Metformin is usually prescribed as first line therapy in patients with T2DM given its beneficial effects on HbA1c, weight, and cardiovascular mortality as well as its relative safety profile [8–12]. In addition, it has a very low cost compared with newer treatments. The place of second line medicines in combination with metformin is now becoming clearer following recent studies and meta-analyses. For instance in a recent cohort study conducted in the UK, dual treatment with dipeptidyl peptidase-4 inhibitors, also called gliptins, and metformin was associated with a decreased risk in heart failure (38%), cardiovascular disease (33%) and mortality (48%). Triple treatment with metformin, sulphonylureas, and gliptins was also associated with a decreased risk of key outcomes, e.g. 40% reduction for heart failure, 30% for cardiovascular disease, and 51% for all cause mortality [10]. Reductions in cardiovascular events were also seen in other studies [13]. However, other authors are more cautious about the impact of dual therapy with gliptins reducing cardiovascular risk [14]. Recent reviews have further pointed out that gliptins have a neutral effect on cardiovascular outcomes and stroke [15–18]. A crucial area in the management of patients with T2DM is adherence to medicines, which is typically seen as sub-optimal across countries [3,19–21], although studies have suggested greater compliance with metformin and the gliptins versus other combinations [22].

Vildagliptin is a selective dipeptidyl peptidase-4 inhibitor. It acts on the alpha and beta pancreatic cells, preventing incretins degradation. With increased levels of these substances, there is a good response of the islets of Langerhans to help with glycemic control through insulin regulation and glucagon [23]. The potential benefits of vildagliptin include a lower incidence of weight gain, hypoglycemia and peripheral oedema compared with other oral hypoglycaemic medicines [24].

The recent beneficial findings with the gliptins including vildagliptin have resulted in the Brazilian public health system being sued in the courts and requested to provide vildagliptin for patients. This is because of the stated goal of universal access to healthcare for all patients in Brazil, with the potential for citizens to take their case to court if they believe they are not being treated appropriately [25]. According to data from the federal government in 2014 more than 460,000 tablets of vildagliptin were acquired, representing an expenditure of nearly US$515,000, with vildagliptin the most requested gliptin in lawsuits. [26]. Brazilian states and municipalities also need to fulfil any regional court rulings further increasing sales. This is why vildagliptin was chosen for this study as opposed to other gliptins.

However, evidence to support the use of vildagliptin in Brazilian context are scarce for both monotherapy and combination therapy. To check the relevance or not of the inclusion of vildagliptin into Brazilian T2DM guidelines, studies are needed to understand the economic impact alongside any clinical benefits. Consequently, we sought to evaluate the cost-effectiveness of vildagliptin monotherapy or combined with any oral hypoglycemic agent for people living with T2DM under Brazilian public health system perspective based on available data from clinical trials and observational studies.

2. Methods

2.1. Search strategy

A systematic search using the MEDLINE, Cochrane Library, LILACS (Latin American and Caribbean Literature in Health Sciences) and CRD (Center for Reviews and Dissemination) databases was conducted in July 2016 to identify published articles assessing the clinical outcomes of vildagliptin for diabetes mellitus Type 2. The search strategies were constructed with terms related to the disease and the medication.

2.2. Eligibility criteria

Two reviewers were involved in assessing the abstracts and disagreements were resolved by consensus. The studies were considered relevant if: (a) they evaluated the treatment of patients with type 2 diabetes mellitus; (b) vildagliptin, combined or not with metformin, was an arm of the study; (c) comprised a follow-up of at least 52 weeks as this is chronic medication with long term outcomes. Following this process, 770 abstracts were identified. Six papers were finally selected for the analysis. Data on efficacy, effectiveness and safety of treatments were extracted. The complications of the disease were classified according to the ICD-10 code, which allows the identification of the associated costs in the databases of the Brazilian health system. The definition of outcomes was considered as reported in the studies. In particular, hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement of < 3.1 mmol/l.

2.3. Economic models

A Markov model was designed considering a hypothetical cohort of T2DM patients, divided into groups according to their pharmacotherapy and the type of studies considered. Based on the transition probabilities between a stage of the disease and another, this type of model allows the simulation of the disease's progression in a population according to time cycles. Consequently, each stage of the disease is considered in the model as a transition state [27].

The main objective of treatment is to keep the patient free of T2DM complications. Secondly, HbA1c levels are expected to remain below 7.0% to help prevent the complications of T2DM including hospitalisation. In this way, the models were developed to assess the efficiency of different approaches in keeping patients free of clinical conditions that result in either secondary or tertiary care. We did not look further at efficiency based on cost per quality adjusted life years (Cost/ QALYs) as no utility data was available in the Brazilian context. This is research for the future.

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To evaluate the retention capacity of patients at the primary care level, all stages of the disease that require specialized care were considered absorbent states. Absorbent states are those in which the patient does not progress to another state within the built hypothetical cohort.

In this study, each cycle has one-year duration and the model comprises a time horizon of 10 years that starts with the mean age of patients reported in the literature. In the first model cycle, the hypothetical cohort's population is comprised of individuals with T2DM, HbA1c higher than 7.0% and no complications from the disease. Transition from the first to the second cycle, and successively, takes place according to the probabilities of transition from each state.

Models were composed of transition states, mutually exclusive, which correspond to the possible stages of the disease. Consequently, transitions were considered from T2DM no complications to other states as reported in studies directly comparing vildagliptin with other therapeutic alternatives, combined or not with metformin.

Transition probabilities are developed with data on disease's progression and the efficacy or effectiveness of the medicines in question. The relevant information was obtained from randomized clinical trials and retrospective or prospective observational studies with a minimum follow-up of 52 weeks. Studies with short follow-ups were not used because in this period there is a greatest reduction in HbA1c and then, its elevation is observed. Studies with a minimum follow-up of 52 weeks best represent sustained levels of HbA1c. Consequently, study selection was made based on this criterion in our models.

Model 1 was built to evaluate the cost-effectiveness of vildagliptin 50 mg b.i.d. monotherapy, compared to metformin 850 mg b.i.d. monotherapy, to avoid the occurrence of hypoglycemic events according Schweizer et al (2007) [28]. In Model 2, the cost-effectiveness of vildagliptin 50 mg b.i.d. and metformin 850 mg b.i.d. in combination was estimated to avoid the occurrence of complications, such as those documented on the clinical trials of Bolli et al (2009) [29], Ferrannini et al (2009) [30] and Filozof (2010) [31]. These studies compared this combination to, respectively, pioglitazone 30 mg per day, glimepiride 2 to 6 mg per day and gliclazide 320 mg per day, all combined with metformin. In Model 3, we considered data from observational studies of Mathieu et al (2013) [32] and Montilla et al (2014) [33] to estimate the cost-effectiveness of vildagliptin-containing treatments compared to regimens in which do not have this medicine. Mathieu et al (2013) reported the comparative effectiveness of metformin combined with vildagliptin or to any other oral hypoglycemic agent. In the study of Montilla et al (2014), the populations were divided by those that used vildagliptin and those that had not used vildagliptin, combined or not with any other oral hypoglycemic agent. There was no dose setting in these two studies.

In Model 1, the transition states were the discontinuation of the treatment due to adverse events, HbA1c higher than 7.0%, hypoglycemia and death. Model 2 considered the same states of Model 1 with the addition of acute coronary syndrome, congestive heart failure, stroke, transient ischemic attacks and peripheral arterial disease. In Model 3, as this was derived from observational studies, hypoglycemia, renal insufficiency, stroke, pneumonia, pericardial effusion, leukemia, colon adenoma, colon cancer, bladder cancer, breast cancer and death were considered (Table 1).

Table 1. Annual probabilities and costs for the evaluation of vildagliptin-containing treatments for Type 2 Diabetes Mellitus.

TRANSITION PROBABILITIES

	Value	Distribution	Reference
Model 1 variables			
Discontinuation of metformin	0.0714	beta[0.0669;0.8701]	Schweizer 2007
Discontinuation of vildagliptin	0.0424	beta[0.0395;0.8930]	Schweizer 2007
Hypoglycemia – metformin	0.0040	beta[0.0016;0.4032]	Schweizer 2007
Hypoglycemia – vildagliptin	0.0058	beta[0.0036;0.6139]	Schweizer 2007
HbA1c > 7,0% – metformin	0.6586	beta[0.6665;0.3454]	Schweizer 2007
HbA1c > 7,0% – vildagliptin	0.7476	beta[0.7502;0.2533]	Schweizer 2007
Model 2 variables			
TIA – control	0.0036	beta[0.0014;0.4020]	Bolli 2009
TIA – vildagliptin	1.00E-06	beta[2.168E–10;0.0002]	Bolli 2009
Stroke – control	0.0054	beta[0.0045;0.8343]	Bolli 2009, Ferrannini 2009
Stroke – vildagliptin	0.0006	beta[0.0002;0.3955]	Bolli 2009, Ferrannini 2009
PAD – control	0.0007	beta[0.0003;0.3961]	Ferrannini 2009
PAD – vildagliptin	1.00E-01	beta[1.016E–09;0.0010]	Ferrannini 2009
Discontinuation of control	0.0709	beta[0.0705;0.9234]	Ferrannini 2009, Filozof 2010
Discontinuation of vildagliptin	0.0537	beta[0.0531;0.9352]	Ferrannini 2009, Filozof 2010
Hypoglycemia – control	0.1095	beta[0.1091;0.8877]	Bolli 2009, Ferrannini 2009, Filozof 2010
Hypoglycemia – vildagliptin	0.0137	beta[0.0129;0.9317]	Bolli 2009, Ferrannini 2009, Filozof 2010
Heart failure – control	0.0014	beta[0.0007;0.5108]	Ferrannini 2009
Heart failure – vildagliptin	0.0014	beta[0.0007;0.5065]	Ferrannini 2009
HbA1c > 7,0% – control	0.6802	beta[0.6845;0.3219]	Filozof 2010
HbA1c > 7,0% – vildagliptin	0.7037	beta[0.7078;0.2980]	Filozof 2010
ACS – control	0.0048	beta[0.0040;0.8262]	Bolli 2009, Ferrannini 2009
ACS – vildagliptin	0.0036	beta[0.0026;0.7411]	Bolli 2009, Ferrannini 2009
Model 3 variables			
Colon adenoma – vildagliptin	0.0001	beta[0.0068;92.3680]	Montilla 2014
Stroke – control	3.2E-05	beta[0.0002;7.6215]	Montilla 2014
Stroke – vildagliptin	0.0001	beta[0.0068;92.3680]	Montilla 2014
Bladder cancer – vildagliptin	0.0001	beta[0.0068;92.3680]	Montilla 2014
Colon cancer – control	0.0001	beta[0.0025;38.9946]	Montilla 2014
Colon cancer – vildagliptin	0.0001	beta[0.0068;92.3680]	Montilla 2014
Breast cancer – control	0.0001	beta[0.0025;38.9946]	Montilla 2014
Pericardial effusion – control	3.2E-05	beta[0.0002;7.6215]	Montilla 2014
Hypoglycemia – control	0.0117	beta[0.0118;0.9919]	Mathieu 2013
Hypoglycemia – vildagliptin	0.0025	beta[0.0024;0.9448]	Mathieu 2013
Renal failure – vildagliptin	0.0001	beta[0.0068;92.3680]	Montilla 2014
Leukemia – control	0.0001	beta[0.0025;38.9946]	Montilla 2014
Leukemia – vildagliptin	0.0001	beta[0.0068;92.3680]	Montilla 2014
Pneumonia – control	0.0001	beta[0.0025;38.9946]	Montilla 2014

COSTS (R$)[a]

Models variables			
Outpatient T2DM	26.2162	gamma[0.2705;0.0103]	SIA
Outpatient hypoglycemia	30.9205	gamma[0.4238;0.0137]	SIA
Inpatient T2DM	486.0846	gamma[0.5056;0.0010]	SIH
Inpatient hypoglycemia	63.8444	gamma[0.9194;0.0144]	SIH
Metformin (tablet)	0.0580	gamma[19.1832;330.4888]	BPS
Salary CHA	185.3712	gamma[38.4035;0.2072]	PBH
Salary HSA	317.7851	gamma[6.2297;0.0196]	PBH
Salary nurse	767.5083	gamma[7.0584;0.0092]	PBH
Salary doctor	2,725.5172	gamma[4.2581;0.0016]	PBH
Salary HST	277.2010	gamma[9.3583;0.0338]	PBH
Salary HSST	617.8480	gamma[4.7421;0.0077]	PBH
Vildagliptin (tablet)	1.9171	gamma[2,215.93;1,155.8974]	BPS
Model 2 variables			
Outpatient TIA	32.6335	gamma[0.7721;0.0237]	SIA
Outpatient stroke	44.1113	gamma[0.5516;0.0125]	SIA
Outpatient PAD	52.9475	gamma[0.4524;0.0085]	SIA
Outpatient heart failure	117.2197	gamma[0.2056;0.0018]	SIA
Outpatient ACS	304.3038	gamma[1.3264;0.0044]	SIA
Inpatient TIA	953.1707	gamma[0.2602;0.0003]	SIH
Inpatient stroke	1,215.7729	gamma[0.2911;0.0002]	SIH
Inpatient PAD	2,526.9404	gamma[0.7360;0.0003]	SIH
Inpatient heart failure	1,552.1003	gamma[0.1607;0.0001]	SIH
Inpatient ACS	3,773.6034	gamma[0.7505;0.0002]	SIH
Control (tablet)	0.4054	gamma[44.497;109.7738]	BPS
Model 3 variables			
Outpatient colon adenoma	132.2865	gamma[5.7146;0.0432]	SIA
Outpatient stroke	44.1113	gamma[0.5516;0.0125]	SIA
Outpatient bladder cancer	318.6474	gamma[0.6069;0.0019]	SIA
Outpatient colon cancer	915.8832	gamma[1.0348;0.0011]	SIA
Outpatient breast cancer	518.3841	gamma[1.8797;0.0036]	SIA
Outpatient pericardial effusion	44.1064	gamma[0.7066;0.0160]	SIA
Outpatient renal failure	62.8281	gamma[0.1348;0.0021]	SIA
Outpatient leukemia	168.0535	gamma[1.2572;0.0075]	SIA
Outpatient pneumonia	26.7389	gamma[0.4439;0.0166]	SIA
Inpatient colon adenoma	3,481.8368	gamma[1.6286;0.0005]	SIH
Inpatient stroke	1,215.7729	gamma[0.2911;0.0002]	SIH
Inpatient bladder cancer	1,227.4688	gamma[0.4330;0.0004]	SIH
Inpatient colon cancer	1,157.0266	gamma[0.6953;0.0006]	SIH
Inpatient breast cancer	781.2555	gamma[0.3663;0.0005]	SIH
Inpatient pericardial effusion	2,745.2068	gamma[0.5862;0.0002]	SIH
Inpatient renal failure	1,835.3242	gamma[0.2704;0.0001]	SIH
Inpatient leukemia	2,494.5476	gamma[0.4101;0.0002]	SIH
Inpatient pneumonia	1,008.7475	gamma[0.2766;0.0003]	SIH
Control (tablet)	1.9082	gamma[37,629.38;1,9719.8255]	BPS

[a] Monetary amounts in Brazilian currency. Conversion factor to purchasing power parity: 1.73 (local currency per international $), World Bank, 2014.
ACS: acute coronary syndrome; BPS: Brazilian Health Prices Database; CHA: community health agent; T2DM: type 2 diabetes mellitus; HbA1c: glycosylated hemoglobin A1c; HSA: health service agent; HSST: health service superior technician; HST: health service technical; PAD: peripheral artery disease; PBH: Municipality of Belo Horizonte; PE: pericardial effusion; SIA: Brazilian Outpatient Information System; SIH: Brazilian Hospital Information System; TIA: transient ischemic attack.

In models 1 and 2, patients who discontinued treatment due to adverse events, or remained with HbA1c higher than 7.0%, followed the hypothetical cohort with rescue therapy considering the same transition probabilities for the other stages, except for the increase of, respectively, 10% and 30% in the risk of death. Treatment discontinuation due to adverse events was considered only in the first two years of the cohort. In Model 3, because there are insufficient observational data to model these two clinical conditions, the patients remained in the T2DM no complications stage until they went on to some modelled complication.

According to the literature, the average ages of entry for patients in the hypothetical cohorts were 53, 58 and 62 years for models 1, 2 and 3, respectively. Since death probabilities in these studies were lower compared to the Brazilian population and lower for vildagliptin compared to controls, the overall death probability for each age in the Brazilian population was considered, in 2014, for the groups treated with vildagliptin. For the comparator groups, the same probability has been multiplied by the ratio of its superiority in relation to the value of vildagliptin obtained in the study (Table 2).

Table 2. Annual probability of death used in the models for evaluation of vildagliptin-containing treatments for Type 2 Diabetes Mellitus.

Age	Model 1[a]		Model 2[b]		Model 3[c]	
	Vildagliptin	Metformin	Vildagliptin	Control	Vildagliptin	Control
53	0.0068	0.0140				
54	0.0073	0.0150				
55	0.0078	0.0161				
56	0.0084	0.0173				
57	0.0090	0.0186				
58	0.0097	0.0199	0.0097	0.0131		
59	0.0104	0.0214	0.0104	0.0140		
60	0.0111	0.0229	0.0111	0.0150		
61	0.0119	0.0246	0.0119	0.0161		
62	0.0128	0.0265	0.0128	0.0173	0.0128	0.0155
63			0.0139	0.0187	0.0139	0.0166
64			0.0150	0.0203	0.0150	0.0178
65			0.0163	0.0220	0.0163	0.0191
66			0.0176	0.0238	0.0176	0.0206
67			0.0192	0.0259	0.0192	0.0222
68					0.0209	0.0241
69					0.0228	0.0261
70					0.0248	0.0283
71					0.0270	0.0307

[a] Vildagliptin monotherapy vs. metformin monotherapy.
[b] Vildagliptin combined with metformin vs. metformin combined with other hypoglycemic agent.
[c] Dual vildagliptin-containing treatment vs. other dual treatment.

To balance the timeliness and data consistency, all monetary values used are for 2014. Medicines prices considered in the study were taken from the Integrated System of Administration and General Services (Siasg) through the Health Prices Database (BPS) [26]. Through the Hospital Information System (SIH) [34] and the Outpatient Information System (SIA) [35], the average costs for hospitalisation and outpatient services for each identified transition states were obtained. For these costs, means and standard deviations were calculated (Table 1).

Based on the city of Belo Horizonte, Minas Gerais, as a representative city within Brazil, average remuneration levels were obtained for health professionals who participate directly in the care of patients affected by T2DM in primary care. This includes doctors, nurses, community health care workers as well as technicians and other relevant health care workers treating these patients technician [36]. Considering a monthly follow, half an hour per month was considered the equivalent of the remuneration of each professional for the total annual value (Table 1).

Models 1 and 2 considered rescue therapy in cases of discontinuation due to adverse events and HbA1c higher than 7.0%. For Model 1, this means adding metformin 850 mg b.i.d. to vildagliptin 50 mg b.i.d. and the increase of monotherapy with metformin 850 mg from b.i.d. to t.i.d. In Model 2, metformin 850 mg increased from b.i.d. to t.i.d in combination with vildagliptin or control (pioglitazone, glimepiride or gliclazide).

In health technology economic evaluations, the use of a discount rate in cost and effectiveness analyses is recommended. Where there is often a difference in time between the investment in health service resources and benefits in health associated with the investment, we used the arbitrary rate of 5% for costs and effects, recommended by the Ministry of Health in Brazil when the analysis is for longer than one year [37].

Effectiveness was measured in life years (LY). A LY was computed for each cycle in which patients remained free of complications that resulted in either secondary or tertiary care. We also considered, according to each cycle, costs related to their transition states.

At the end of the hypothetical cohort, costs and effectiveness were calculated according to the different interventions. For each intervention, the cost-effectiveness ratios (CER) were calculated. CER will correspond to the monetary value that will need to be invested in a particular treatment in order to obtain a LY under primary care. In this cost-effectiveness analysis, currency values were adjusted for purchasing power parity (PPP), whose conversion factor was approximately 1.73 (local currency for international $) in 2014 [38]. Adjusted values were expressed with currency symbol $.

In this study, the incremental cost-effectiveness ratio (ICER) reflects the cost of a LY gained or one hypoglycemia episode avoided compared to other treatments. ICER is the ratio of the differences in cost and effectiveness between the assessed therapeutic alternatives. An intervention is considered cost-effective in Brazil if the ICER value is lower than the Brazilian gross domestic product (GDP) per capita, equivalent to $ 16,210.24 in 2014 [39].

Results obtained by economic evaluations in health are subjected to uncertainties, which are mainly justified by the limited data available [37]. In this study, a probabilistic sensitivity analysis was conducted to assess how far the uncertainties of variables interfere with an outcome. Consequently, a Monte Carlo simulation was performed to generate a sample of

1,000 interactions between variables considering willingness to pay between half and one GDP per capita. Beta distributions were used for each progression data of the disease and gamma distributions for each allocated costs. For presenting random values between 0 and 1, beta distribution has its recommended use to simulate distribution of transition probabilities of hypothetical cohorts. However, for the cost data, which are not random and cannot be negative, the use of gamma distribution for sensitivity analysis is recommended [40].

3. Results

At the end of ten years, 22.2% of patients who were treated with vildagliptin monotherapy and 27.0% of those using only metformin remained without complications and with HbA1c levels lower than 7.0%. For treatments in combination, proportions were 23.3% and 15.2% for metformin associated with, respectively, vildagliptin and control, i.e. pioglitazone, glimepiride or gliclazide. Considering observational data, 81.3% and 71.9% of patients who received vildagliptin and control, respectively, remained without complications (Table 3). Most of patients showed HbA1c higher than 7.0% at the end of follow-up in models where this clinical situation was a transition state. Comparing monotherapies, the proportion of patients treated with vildagliptin in this situation was 26.8% higher compared to metformin. As for the association between vildagliptin and metformin, the superiority was 56.1% compared to control (Table 3).

Table 3. Patients proportion in each transition state at the end of the hypothetical cohort.

Stage	Model 1[a]		Model 2[b]		Model 3[c]	
	Vildagliptin	Metformin	Vildagliptin	Control	Vildagliptin	Control
T2DM without complications	0.2223	0.2696	0.2330	0.1521	0.8126	0.7193
Discontinuation for adverse events	0.0000	0.0000	0.0000	0.0000		
HbA1c > 7,0%	0.6621	0.5223	0.5580	0.3574		
Hypoglycemia	0.0137	0.0120	0.0361	0.2590	0.0230	0.1007
Death	0.1019	0.1960	0.1378	0.1513	0.1605	0.1771
Acute coronary syndrome			0.0223	0.0242		
Heart failure			0.0090	0.0073		
Stroke			0.0037	0.0272	0.0007	0.0003
Transient ischemic attack			0.0000	0.0180		
Peripheral artery disease			0.0000	0.0036		
Renal failure					0.0007	0.0000
Colon cancer					0.0007	0.0006
Colon adenoma					0.0007	0.0000
Leukemia					0.0007	0.0006
Bladder cancer					0.0007	0.0000
Pneumonia					0.0000	0.0006
Breast cancer					0.0000	0.0006
Pericardial effusion					0.0000	0.0003

[a] Vildagliptin monotherapy vs. metformin monotherapy.
[b] Vildagliptin combined with metformin vs. metformin combined with other hypoglycemic agent.
[c] Dual vildagliptin-containing treatment vs. other dual treatment.

Among the complications evaluated in the model, acute coronary syndrome showed a higher proportion at the end of the model, with 2.2% for patients who were treated with the

combination of vildagliptin and metformin and 2.4% for controls. A higher proportion than 1% was observed only for stroke and transient ischemic attack in patients treated with metformin associated with control. In all models, the proportion of death was lower in groups treated with vildagliptin, with inferiority ranging between 8.9% and 48.0% (Table 3).

In all models, the total cost of patients' treatment using vildagliptin was greater than those who used controls. Values were 27.0%, 22.9% and 12.2% higher considering the models 1, 2 and 3, respectively. On the other hand, treatments containing vildagliptin offered higher LYs with no complications, being, respectively, 4.3%, 19.8% and 5.3% longer than controls. Differences between cost and effectiveness of treatment with vildagliptin were higher in all comparisons, being 21.7% higher in the comparison of monotherapy with metformin, 2.6% higher between combinations and 6.4% above considering observational data (Table 4).

Table 4. Cost-effectiveness of vildagliptin-containing treatments for Type 2 Diabetes Mellitus

Treatment	Cost ($)	Incremental cost ($)	Effectiveness (LY)	Incremental effectiveness (LY)	CER ($)	ICER ($)
Model 1[a]						
Metformin	23,089.40		7.23		3,159.55	
Vildagliptin	29,228.68	6,139.27	7.54	0.31	3,878.25	19,735.91
Model 2[b]						
Control	24,123.31		6.01		4,012.62	
Vildagliptin	29,651.22	5,527.91	7.20	1.19	4,119.26	4,659.62
Model 3[c]						
Control	26,175.59		6.92		3,783.67	
Vildagliptin	29,373.38	3,197.80	7.29	0.37	4,029.03	8,587.09

[a] Vildagliptin monotherapy vs. metformin monotherapy.
[b] Vildagliptin combined with metformin vs. metformin combined with other hypoglycemic agent.
[c] Dual vildagliptin-containing treatment vs. other dual treatment.
$: Currency values were adjusted for purchasing power parity (PPP). Conversion factor to purchasing power parity: 1.73 (local currency per international $), World Bank, 2014; LY: life years.

ICER of vildagliptin monotherapy compared to metformin was US$19,735.91, which means 21.7% above the cost-effectiveness threshold set for this study based on the Brazilian context. On the other hand, it was below GDP per capita in the other two comparisons. Considering the comparison between metformin combined with vildagliptin or other medicines, the ICER was equivalent to 28.7% of the considered threshold, totalizing $4,659.62. For the comparison involving observational data, the ICER was from $8,587.09, corresponding to 53.0% of GDP per capita (Table 4).

According to the sensitivity analysis, considering willingness to pay between half and one GDP per capita, none of the simulations for treatment with vildagliptin had a higher

proportion of presenting a lower CER compared to controls. The vildagliptin CER was lower than the control CER in 0.5% to 12.2% of the simulations in Model 1, 23.4% to 28.9% in Model 2 and 3.0% to 5.0% in Model 3 (Figure 1).

Figure 1. Probabilistic sensitivity analysis for the cost-effectiveness of vildagliptin-containing treatments for Type 2 Diabetes Mellitus. (a) Vildagliptin monotherapy vs. metformin monotherapy; (b) Vildagliptin combined with metformin vs. metformin combined with other hypoglycemic agent; (c) Dual vildagliptin-containing treatment vs. other dual treatment.
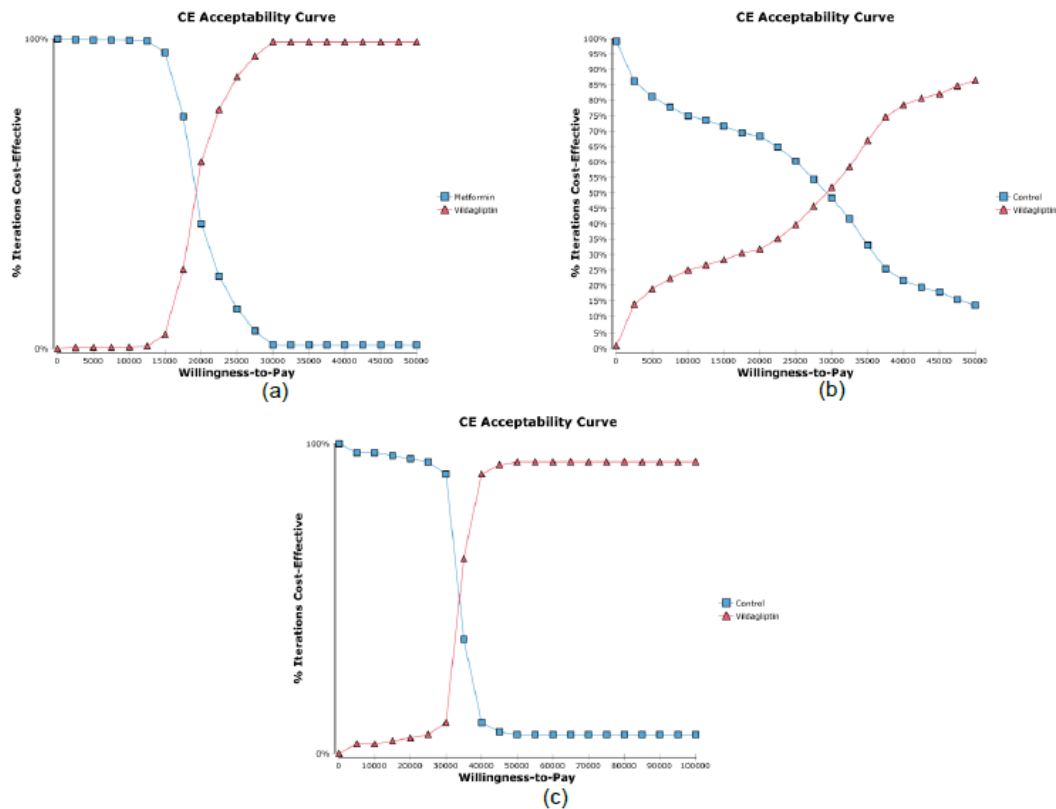
In the ICER analysis, these were higher than the willingness to pay in most simulations involving treatment with vildagliptin. In addition, in these simulations vildagliptin was more expensive and more effective. The simulations proportion in this situation was 86.8%, 65.9% and 89.0%, respectively, in the models 1, 2 and 3 (Table 5).

Table 5. ICER simulations from the probabilistic sensitivity analysis for the cost-effectiveness of vildagliptin-containing treatments for Type 2 Diabetes Mellitus.

Settings	Proportion (%)		
	Model 1[a]	Model 2[b]	Model 3[c]
IE>0, IC<0	0.0	0.8	0.0
IE>0, IC>0, ICER<GDP per capita	12.2	28.1	5.0
IE<0, IC<0, ICER>GDP per capita	0.0	0.0	0.0
IE>0, IC>0, ICER>GDP per capita	86.8	65.9	89.0
IE<0, IC<0, ICER<GDP per capita	0.0	0.0	0.0
IE<0, IC>0	1.0	5.2	6.0
IE=0, IC=0	0.0	0.0	0.0

[a] Vildagliptin monotherapy vs. metformin monotherapy.
[b] Vildagliptin combined with metformin vs. metformin combined with other hypoglycemic agent.
[c] Dual vildagliptin-containing treatment vs. other dual treatment.
IC: incremental cost; IE: incremental effectiveness; GDP: gross domestic product

4. Discussion

Despite treatments with vildagliptin offering longer life without complications, differences compared to controls were small in the comparison with metformin or among observational data. Difference between treatments combined with metformin was the largest, meaning approximately a year and 2 months longer life for patients who received vildagliptin. However in all comparisons, treatment's costs with vildagliptin were higher in relation to controls especially since metformin is available as a low cost generic in Brazil.

Considering data used and willingness to pay, the use of vildagliptin in T2DM treatment is not cost-effective using the definitions in Brazil. This is even more so if a cost/QALY ICER was used, which is normally the metric used by health authorities using cost effectiveness evaluations in their decision making [8,41–45]. Compared with metformin, the ICER for vildagliptin was higher than GDP per capita. Comparing its combination with metformin and with other drugs, despite the ICER being lower than GDP per capita, it is predominantly higher than the willingness to pay on the uncertainties of variables used. For the same reason, treatments involving vildagliptin cannot be considered cost-effective based on available data.

As previously mentioned, oral hypoglycemic agents provided by the Brazilian public health system are metformin, glibenclamide and gliclazide. In addition to these, regular and NPH insulins are included in the essential drug lists for treatment of people living with Diabetes Mellitus. Some Brazilian states have also included insulin analogues in their supply lists [25]. Considering the comparison between monotherapies, vildagliptin cannot currently be recommended as a substitute of metformin as monotherapy in line with current treatment guidelines [10,13,22]. In the assessment of metformin combinations, it is not possible to conclude about the superiority of vildagliptin compared to gliclazide, because we needed to include data from other medicines in vildagliptin-comparator modelling. The study of Filozof et al (2010) was the data source of the combination of gliclazide and metformin, whose

variables extracted were HbA1c > 7,0%, hypoglycemia, discontinuation due to adverse events and overall death [27]. In fact, the mean values of this study were lower for the combination of metformin and gliclazide than vildagliptin combined with metformin, except for hypoglycemia. The similarity between the combinations in HbA1c lowering was the conclusion of the study.

Comparisons involving observational data were made even though there is acknowledged heterogeneity in the patients enrolled. Two studies were used, one of which included any oral hypoglycemic agent as a control and the other considered sitagliptin – a dipeptidyl peptidase-4 inhibitor currently not provided by Brazilian public health system. Furthermore, most of data used in the model was extracted from this study, being the only data source of progression to complications. Consequently, in this evaluation, vildagliptin is basically compared to other DPP-4 inhibitor. Therefore, its ICER should be interpreted with caution for inclusion in the health system drugs list.

Health economic models are a simplification of what is considered as treatment and actual clinical prognoses. In this way, treatment of a disease is not typically fully addressed in a multifactorial complexity. Economic analysis based on models helps in decision making by those responsible for coordinating programs and health services within finite resources. Factors, parameters and assumptions considered in the model, as well the non-modeled, should be considered for decision making.

We accept a number of limitations with our analysis and review. These include the fact that the effectiveness and efficacy data obtained were from non-Brazilian as there was no clinical trial or observational data including patients from Brazil populations. We also only included studies with longer term follow-up for the reasons discussed in the methodology. In addition, available studies typically only had a short follow-up period. In this way, clinical data were extrapolated until the end of the hypothetical cohort. Literature on the efficacy and effectiveness of vildagliptin is scarce, although approved by the Brazilian regulatory agency in 2007. Most studies comprise only 24 weeks of follow-up. Richter et al (2008), in a systematic review concerning DPP-4 inhibitors for the treatment of T2DM published by Cochrane Collaboration, indicated the urgent need for data about safety and follow up for long periods to aid decision making [46].

Shortage of this data is acknowledged in the models presented, implying the potential underestimation of disease complications and treatment costs. Waugh et al (2010), in a systematic review and economic evaluation of new medications for glycemic control in the UK perspective [47], included only one 24-week study, comparing metformin combined with vildagliptin or pioglitazone. The results of 52 weeks were published by Bolli et al (2009) and included in the models presented in this study [25]. In the economic model, patients' starting age was 58 years and the follow-up duration was 40 years. Effectiveness ranged from 8.56 years for men and 9.43 years for women. Considering that life expectancy of Brazilian population is lower than in UK, and that the model presented here has a time horizon of 10 years, it seems reasonable that effectiveness results ranged between 6.01 and 7.54 years.

We are also aware that we only look at ICERs based on LY saved and not cost/QALYs in our research. From the perspective of Portuguese health system, Viriato et al (2014) evaluated the cost-effectiveness between vildagliptin and metformin compared to metformin with sulphonylurea in a period of 40 years of follow-up. For this, they used the UKPDS Outcomes Model - model based on data from 30-year United Kingdom Prospective Diabetes Study

carried out in English population [48]. Therapeutic alternatives demonstrated similar clinical results, with an increase of 2.3% in the quality adjusted life years with the use of vildagliptin (5.7681 vs. 5.6401). However, this alternative increased spending by 8.8% (€14,409 vs. €13,248), providing an ICER of €9,072 [49]. Costs and effectiveness of the different therapeutic alternatives were lower than observed in our study. This may be due to the fact that Viriato et al did not consider costs with health professionals in their model, but considered different clinical complications and having adjusted life years to their quality.

Regarding the Brazilian context, an evaluation was recently performed with saxagliptin compared to rosiglitazone and pioglitazone, all combined with metformin, from the perspective of private health insurance companies. This study considered the clinical and economic data of insurers' records over a three-year time horizon. In all comparisons, the authors considered saxagliptin was cost-saving when combined with metformin versus the glitazone combinations. However, they did not research saxagliptin as monotherapy [50]. In a recent systematic review summarizing the results of the cost-effectiveness assessments of gliptins either as monotherapy or in combination, the authors concluded that gliptins combined with metformin are a cost-effective option compared to sulfonylureas and insulin. However, the quality of these studies was low and there are few studies free of conflicts of interest [51].

In another recent review, the authors considered gliptins cost-effective as add-on to metformin compared to sulfonylureas. However, the gliptins were not cost-effective when compared to GLP-1 receptor agonists and insulin analog glargine [52]. There were also concerns that the analyses were based on studies financed by the manufacturers. In a further cost-effectiveness evaluation of combined treatments with metformin, despite no significant differences in effectiveness and costs, dapagliflozin was considered cost-effective compared to gliptins from the UK Healthcare System Perspective [53].

In view of the current cost of US$1.11 for a vildagliptin tablet and US$0.03 for a metformin tablet in Brazil, only a dramatic reduction in the price of vildagliptin would make this treatment become cost-effective in Brazil as monotherapy. Despite recent publications on the benefits of dual treatment with gliptins and metformin, doubts still remain about the choice of vildagliptin over other gliptins as well as the overall safety of the gliptins [14-18]. The lack of safety data precludes the proper assessment of complications associated with this disease or other potential events associated with vildagliptin and their costs. Since the first register of vildagliptin, there has been concern about their limited effectiveness and the potential increased risk of patients experiencing cardiac and liver disorders, infections, pancreatitis, anaphylactic reactions, intestinal obstruction, bullous pemphigoid and neoplasms [54]. Because of the uncertainties about its safety, the FDA has not currently registered vildagliptin. As a result, still a concern in Brazil.

More studies of comparative effectiveness and safety are needed, using real-life data to improve our knowledge of vildagliptin especially in Latin American countries such as Brazil. Long-term evidence on clinical outcomes, safety and economic implications of new antidiabetic drugs are limited in the literature. Such evidence is even more limited on the direct comparison between medicines not grouped by pharmacological class [55]. Budgetary and logistical impact assessments will also aid decision making.

5. Conclusion

Considering the clinical and monetary data from the treatment of T2DM patients, monotherapy with vildagliptin is not cost-effective compared to the monotherapy with metformin. In combination with metformin, vildagliptin demonstrated a low ICER in relation to other controls. However, sensitivity analysis identified a higher probability of this value to be more expensive than the willingness to pay threshold in Brazil, as well as in the analysis involving observational data comparing vildagliptin combinations in relation to other combinations between two oral hypoglycemic agents. Consequently, the incorporation of vildagliptin or its combination with metformin is currently not recommended for the Brazilian Health Care System. This may change as more long term data becomes available, especially safety data given current concerns, and ICER thresholds change. In addition, more studies of comparative effectiveness are needed using Brazilian real-life data to further assess the safety, effectiveness and cost-effectiveness of vildagliptin especially in combination with metformin. This also includes the generation of cost-utility data in the future. These are considerations for the future.

6. Expert commentary

The prevalence and expenditure on patients living with type 2 diabetes mellitus (T2DM) is increasing challenging healthcare systems especially those striving to provide universal healthcare. Typically guidelines for these patients, including Brazil, have metformin and sulfonylureas such as glibenclamide and gliclazide first line followed by insulin if needed. More recently, vildagliptin as monotherapy, or combined with metformin, has the potential to help achieve glycemic control as well as decrease episodes of hypoglycaemia and peripheral edema. However, there are concerns with its cost-effectiveness in Brazil where new treatments are considered as cost-effective at between half and one GDP per capita. Developed models showed that the use of vildagliptin increased life by a mean of 0.31 years compared to metformin and 1.19 more life years when combined with metformin when compared to other metformin combinations. However, despite reducing the occurrence of hypoglycemic events and increasing life expectancy, treatments for patients with T2DM containing vildagliptin are not currently considered cost-effective from the perspective of the Brazilian Health System.

7. Five-year perspective

It is likely that metformin and sulfonylureas will remain first choice treatments for patients with T2DM in Brazil over the next 5 years given the published evidence and their continued low costs. For patients where these medications are no longer sufficient for glycemic control, insulin administration or additional oral treatments with the gliptins such as vildagliptin will increasingly be used. New studies will provide insights into the safety, the risk of anaphylactic reactions as well as the potential for increased infections, pancreatitis and bullous pemphigoid with vildagliptin. However, unless new evidence points to an improved safety profile and effectiveness, it is unlikely that vildagliptin will be included within the Public Health System in Brazil unless the economic thresholds appreciably change.

8. Key issues:

- The prevalence and costs associated with Type 2 diabetes is increasing. New treatents are welcomed; however they need to be cost-effective to be affordable within public healthcare systems
- Considering the willingness to pay up to a per capita GDP, vildagliptin monotherapy is not currently considered cost-effective compared to metformin monotherapy within the Brazilian public healthcare system
- Despite the low ICER of vildagliptin combined with metformin compared to other metformin combinations, we identified a higher probability of this value to be above the willingness to pay threshold based on Markov models and simulations
- Involving observational data, despite the low ICER, vildagliptin-containing treatments have again a lower probability to be below the cost-effectiveness threshold.
- Incorporation of vildagliptin or its combination with metformin is not currently recommended for the Brazilian Health System. This may change, especially for vildagliptin combined with metformin, once more long-term safety and outcome are reported.

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