Cost-effectiveness and budget impact of saxagliptine as additional therapy to metformin for the treatment of diabetes mellitus type 2 in the Brazilian private health system

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Summary

Objectives: To compare costs and clinical benefits of three additional therapies to metformin (MF) for patients with diabetes mellitus type 2 (DM2). **Methods:** A discrete event simulation model was built to estimate the cost-utility ratio (cost per quality-adjusted life years [QALY]) of saxagliptine as an additional therapy to MF when compared to rosiglitazone or pioglitazone. A budget impact model (BIM) was built to simulate the economic impact of saxagliptine use in the context of the Brazilian private health system. **Results:** The acquiring medication costs for the hypothetical patient group analyzed in a time frame of three years were R$ 10,850,185, R$ 14,836,265 and R$ 14,679,099 for saxagliptine, pioglitazone and rosiglitazone, respectively. Saxagliptine showed lower costs and greater effectiveness in both comparisons, with projected savings for the first three years of R$ 3,874 and R$ 3,996, respectively. The BIM estimated cumulative savings of R$ 417,958 with the repayment of saxagliptine in three years from the perspective of a health plan with 1,000,000 covered individuals. **Conclusion:** From the perspective of private paying source, the projection is that adding saxagliptine with MF save costs when compared with the addition of rosiglitazone or pioglitazone in patients with DM2 that have not reached the HbA1c goal with metformin monotherapy. The BIM of including saxagliptine in the reimbursement lists of health plans indicated significant savings on the three-year horizon.

Keywords: Health economics; diabetes mellitus type 2; health management; therapeutics; pharmacy and therapeutics committee; cost-effectiveness assessment.

Introduction

The prevalence of type 2 diabetes mellitus (DM2) continues to grow around the world and it is considered today a global epidemic. A study of global burden of diabetes mellitus has identified that, in 1995, there were 135 million people with diabetes in the world and there are projections that, in 2025, this figure will reach 300 million[1]. It is estimated that 2/3 of these patients live in developing countries, and countries such as Brazil, India, and China will have twice as many patients with diabetes than the USA[2,3].

Brazilian regional studies observed that DM2 prevalence varies between 7% and 13%[4-7]. However, the only Brazilian study of prevalence at national level was conducted in the late 1980's, showing a prevalence of diabetes in the population of 30-69 years of 7.6%[8]. After two decades other studies were conducted, showing DM2 prevalences of 12.1% in the city of Ribeirão Preto/SP[7], 12.4% in Porto Alegre/RS[9], and 7.1% in Pelotas/RS[7]. The most recent prevalence studies did not include the North, Northeast and Midwest regions of Brazil, which may mean that the estimates currently available do not comprehensively portray the DM2 national reality. Several factors are associated with the observed increase in the prevalence of diabetes mellitus in Brazil and worldwide. The most frequently discussed were increasing life expectancy of the population, changes in lifestyle (including high-fat foods and sedentary lifestyle), and obesity[1,10,11].

As a chronic condition with serious complications and high demand of care, DM2 is an expensive disease. Although published data have shown that improved glycemic control can lead to better health outcomes, fewer than 50% of the Brazilian patients assessed in local studies reached the desired value for HbA1c[12-14]. Thus, strategies directed to a better glycemic control of these patients, including new drugs used in combination with existing hypoglycemic agents, may improve the health *status* of patients with DM, reducing the complications[15,16] and costs associated[17-19]. Saxagliptine (SAX) is a selective inhibitor of dipeptidyl peptidase-4 (DPP-4), whose safety and efficacy have been established in randomized studies that have observed significant reductions in HbA1c in monotherapy or in additional therapy to metformin (MF)[20-23]. In the Brazilian health system, public and private services coexist and account for about USD 70 billion per year, which corresponds to nearly 7.5% of the country's GDP. Currently, 37 million (≈ 20%) Brazilian people have access to the private health system. The economic analysis on health is a well-established method to assess the effectiveness of new drugs, and it is increasingly used as a managerial tool[24,25]. Whereas the data of cost-effectiveness in schemes with SAX for patients who have failed to achieve the goals of HbA1c with MF in Brazil are not available, the objective of this study is to compare the costs and benefits of additional therapies to metformin.

Methods

Decision-making model

A discrete event simulation model was designed to estimate the incremental cost-effectiveness ratio of SAX as an additional therapy to MF versus the addition of rosiglitazone (ROS) or pioglitazone (PIO) in a hypothetical cohort of patients treated with MF without glycemic control. Such models are based on secondary data (obtained through systematic review of the literature) to estimate the outcome of a group of patients with the disease under analysis with each of the comparators, using computational simulation resources.

The model was developed using data derived from the United Kingdom prospective diabetes study (UKPDS), which demonstrated the association between HbA1c, levels of systolic blood pressure, and micro and microvascular complications[15]. The UKPDS outcomes model (a decision model built from the results of UKPDS) simulates the health results throughout the lives of patients with DM2 to predict the occurrence and moment of seven DM-related complications (myocardial infarction [MI], congestive heart failure [CHF], stroke, amputation, terminal stage renal disease [TSRD], and blindness) and calculate the life expectancy and the quality-adjusted life years (QALYs)[26].

The main characteristic of the model type used is the ability to generate a hypothetical cohort of patients, with DM2 (n = 1,000) for each therapeutic approach and assign different demographic profiles and a set of risk factors (body mass index [BMI], total cholesterol, HDL cholesterol, systolic blood pressure, and HbA1c) for each one, allowing the simulation of the behavior of patients treated according to their baseline risk of events. Regarding entry in the model, all patients are in monotherapy with MF with uncontrolled blood glucose. At this stage they start one of the three strategies and their progression and the effect of the treatment are then simulated at one-year intervals, after which the results of health and cost of the treatment are updated. The occurrence of fatal and non-fatal events depends on the demographic profile of the patient, attributed clinical characteristics, and risk equations based on the data in UKPDS. The simulation is run for 1,000 patients and ten repetitions where the mean results are provided for costs and benefits. During the evolution, when patients are above the HbA1c threshold (≥ 7.5%), they receive rescue therapy with NPH insulin and MF. To test the model stability related to the variability and uncertainty in the parameters and assumptions followed, two different strategies were used (univariate sensitivity analysis and probabilistic sensitivity analysis), with a variation of the following parameters: utility values, probability of adverse events, characteristics on baseline and costs. Additional data are available from the authors and can be supplied to interested parties.

Patient profiles and treatment effect

The characteristics on baseline followed in the model are shown in Table 1 and were obtained from analyses of the subgroup of patients on monotherapy with MF in DIAPS79[27], a Brazilian study of clinical outcomes and cost of DM2 on the private health system. The model uses different profiles of efficacy and safety for each comparator expressed by the treatment effect on HbA1c, cardiovascular risk factors and adverse events (Table 1)[28-31]. For the case-base, the decrease in HbA1c in the first year was based on a published meta-analysis[32], the duration of the benefit was established as 12 months, no delay at the beginning of HbA1c modification was assumed, and the slope of the curve was set as 0.759 (defined by a nonlinear function). Both comparators showed similar results in terms of reduction of HbA1c. Consequently, the progression curves overlap over time.

Cost data and utilities weights

The annual cost data inserted in the model are related to the purchase of medicinal products, control of adverse events and treatment of complications for DM2. All costs were discounted at an annual rate of 5%. Medication costs were obtained from official lists and the mean doses of the DIAPS79 study. The source of cost data related to micro and macrovascular complications was also the DIAPS79 study, except for the costs related to the maintenance of patients with TSRD (Table 2), which were not available from that study and were based on assumptions from the repayment of the public health system (as an approximation of values in the private health, due to the lack of specific data).

The utility values are weights attributed to health states and reflect the patients' preferences for each state on a scale of 0 (death) to 1 (best imaginable health state). When an event (complication or death) occurs in the model, the patient receives a factor that is subtracted from the mean utility allocated to patients without complication. The utility reduction coefficients were obtained from UKPDS62, with the exception of TSRD and blindness[33,34]. QALYs were calculated by multiplying the time spent in the *status* of health by the utility of the health *status* (Table 2)[35].

Budget impact model (BIM)

A BIM was designed to simulate the economic impact of using SAX in patients with DM2 and uncontrolled blood glucose in a time frame of three years. The BIM analysis combines epidemiological data, estimates of market share and treatment costs to predict the eligible population and the total investment needed to deliver a new drug to patients. The BIM was designed considering a health plan with 1,000,000 individuals and only the costs relating to the purchase of medicines were considered, since other medical costs are not significantly different among the comparators in short-term time frames. The expected annual cases of DM2 were calculated by applying the Brazilian data of prevalence adjusted by age[7,36] and the annual increment of cases is a result of the ageing of the population and the increased prevalence of the disease among older individuals. Table 2 presents input data for the BIM. To estimate the current market share that would be replaced by SAX, data from a national survey that assesses the sales of medicines in pharmacies in Brazil were combined with the mean dose reported in DIAPS79. The assumption followed was that the market share for SAX would rise from 0.35% in the first year to 1.95% in the third year, mainly due to the replacement of TZDs and, to a lesser extent, due to the replacement of sulfonylurea.

Results

Compared with the addition of ROS to the ongoing therapy with MF, SAX was estimated to avoid 12.3 vascular events (5.3 fatal cases). When compared to PIO, SAX resulted in an incremental benefit of 15.0 vascular events avoided (3.5 fatal cases). The acquisition costs of the medication for the assessed cohort were R$ 10,850,185, R$ 14,836,265, and R$ 14,679,099 for SAX, PIO and ROS, respectively. Hospitalization and treatment of adverse events were the main components of the cost, representing 67.2%, 59.9% and 60.2% of the total costs for SAX, PIO and ROS, respectively. Both comparisons point to the additional therapy of SAX as being cost-saving (more effective and less costly), with projected savings for the first three years of R$ 3,874 and R$ 3,996, respectively (Table 3).

In the univariate sensitivity analysis, SAX remained dominant compared to TZDs after a variation of +/-15% on all selected parameters. HbA1c and costs were the parameters that impacted the model, since the baseline level of HbA1c directly affects the amount of time that patients will remain under treatment with SAX or TZDs. In probabilistic analyses, adding SAX to the MF therapy was dominant in 62.1% and 76.6% of all scenarios versus the addition of PIO or ROS, respectively. Only in 2.2% and 1.5% of the simulations did SAX show less effectiveness and higher costs, enhancing the consistency of the observed results. Additional information (including sensitivity analysis graphs and additional details for results of cost-effectiveness) can be obtained by contacting the authors.

The BIM estimated cumulative savings of R$ 417,958 with the reimbursement of SAX in 3 years. Considering the cost per patient eligible for treatment with SAX, the model estimated annual savings that rise gradually until year three, when it reaches 6.6%. Univariate sensitivity analysis was conducted to assess the impact of the main parameters in the final results (prevalence of DM, market share and drug acquisition costs). A variation range of ± 25% was assumed for the sensitivity analysis but the

Table 1 – Basal characteristics of patients and treatment effect parameters

Basal characteristics

Parameter	Value	Source
Median age (years)	59.77	DIAPS79
% of women	0.58	DIAPS79
Mean duration of DM2 (years)	7.27	DIAPS79
Mean height (meters)	1.61	DIAPS79
% of Afro-caribbean	0.15	DIAPS79
% of smokers	0.10	DIAPS79
Mean HbA1c (%)	6.47	DIAPS79
Mean total cholesterol (mmol/L)	4.44	DIAPS79
Mean HDL cholesterol (mmol/L)	1.22	DIAPS79
Mean systolic BP (mmHg)	123.57	DIAPS79
Mean weight (kg)	78.76	DIAPS79
Clinical history of (%)		
Atrial fibrillation	1.1%	DIAPS79
Peripheral vascular disease	3.3%	DIAPS79
Ischemic heart disease	12.0%	DIAPS79
Myocardial infarction	2.2%	DIAPS79
Congestive heart failure	4.3%	DIAPS79
Stroke	3.3%	DIAPS79
Amputation	0.0%	DIAPS79
Blindness	0.0%	DIAPS79
TSRD	0.0%	DIAPS79

Treatment effect parameters

Parameter	Treatment	Control		Rescue
	MF+SAX*	MF+PIO	MF+ROS	MF+INS§
HbA1c				
Reduction in 1st year	-0.69	-0.64§§	-0.63	-2.10
Months with benefit (1st year)	12	12	12	12
Delay in HbA1c modification	0	0	0	0
Slope (per year)	0.759	0.759	0.759	0.759
Risk factors				
Systolic blood pressure	0	0	0	0
Total cholesterol (mmol/L)	0	0.138	0.27	0
HDL cholesterol (mmol/L)	0	0.159¥	0.08¶	0.07
Weight (kg)	-0.28	1.54	1.54	3.500
Adverse events				
Hypoglycemia				
Symptomatic events	0.01	0	0.01	0.47
Nightly events	0	0	0	0
Serious events	0	0	0	0

DM2, diabetes mellitus type 2; BP, blood pressure; TSRD, terminal stage renal disease; MF, metformin; SAX, saxagliptine; PIO, pioglitazone; ROS, rosiglitazone ; INS, insulin; *DeFronzo[22]; §Yki-Järvinen[28]; §§Mwamburi[31]; ¥Polonsky[29]; ¶Stewart[30].

Table 2 – Costs, utilities weights and input parameters in budget impact model

Direct medical costs				
Therapy	**Annual cost of acquisition**			**Source**
Metformin + saxagliptine	2.133			DIAPS79*
Metformin + pioglitazone	2.889			DIAPS79
Metformin + rosiglitazone	2.859			DIAPS79
Metformin + insulin	1.066			DIAPS79
Adverse event	**Event cost**			**Source**
Serious hypoglycemia	0			Assumption
Symptomatic hypoglycemia	0			Assumption
Nocturnal hypoglycemia	0			Assumption
Complication	**Event cost**	**Maintenance**		**Source**
Ischemic heart disease	7.311	704		DIAPS79
Myocardial Infarction	8.651	704		DIAPS79
Congestive heart failure	4.843	704		DIAPS79
Stroke	7.634	704		DIAPS79
Amputation	2.182	872		DIAPS79
Blindness	0	872		DIAPS79
TSRD	4.438	22.464**		DIAPS79
Health state utility weight	**Value**			**Source**
Baseline	0.885			United Kingdom Research
Utility reduction	**Value**			**Source**
Ischemic heart disease	-0.090			UKPDS 62
Myocardial infarction	-0.055			UKPDS 62
Congestive heart failure	-0.108			UKPDS 62
Stroke	-0.164			UKPDS 62
Pre-blindness	-0.029			UKPDS 62
Blindness	-0.074			Currie 2006
TSRD	-0.263			Currie 2006
Kidney transplant	-0.075			UKPDS 62
Amputation	-0.280			UKPDS 62
BMI	-0.014			UKPDS 62
Parameters for budget impact model ingress				
Parameter	**Year 1**	**Year 2**	**Year 3**	**Source**
Individuals covered	1,000,000	1,000,000	1,000,000	Assumption
Prevalence of DM	4.77%	4.88%	4.99%	Calculated
% of diagnosed among the prevalent cases of DM	76.0%	90.0%	90.0%	Decision resources
% of DM2 among patients w/DM	90.0%	91.1%	91.1%	Winer 2004
% of patients with DM2 w/OGLD	91.1%	53.3%	53.3%	DIAPS79
% of uncontrolled DM2 (HbA1c > 10% of the reference value)	53.3%	76.0%	76.0%	DIAPS79

BMI, body mass index; DM, diabetes mellitus; DM2, diabetes mellitus type 2; TSRD, terminal stage renal disease; *DIAPS79, data on file; **assumption based in 3 hemodialysis sessions per week with a unit cost of R$ 144 per session (source: Official List of Public Health System).

Table 3 – Incremental results of case-base (additional therapy of saxagliptine versus comparators)

	Comparator	Costs (R$)	QALY	Cost/QALY gained
Saxagliptine + Metformin versus Pioglitazone + Metformin	Saxagliptine	33,023	10.55	
	Pioglitazone	37,019	10.42	
	Incremental			Dominant
	Comparator	**Costs (R$)**	**LYG**	**Cost/QALY gained**
	Saxagliptine	33,023	12.17	
	Pioglitazone	37,019	12.16	
	Incremental			Dominant
	Comparator	**Costs (R$)**	**QALY**	**Cost/QALY gained**
Saxagliptine + Metformin versus Rosiglitazone + Metformin	Saxagliptine	33,023	10.55	
	Rosiglitazone	36,898	10.41	
	Incremental			Dominant
	Comparator	**Costs (R$)**	**LYG**	**Cost/LYG gained**
	Saxagliptine	33,023	12.17	
	Rosiglitazone	36,898	12.15	
	Incremental			Dominant

QALY, quality-adjusted life years; LYG, life year gained.

conclusion of SAX as an economically viable option remained practicable even by varying the parameter with the greatest impact on final results (acquisition cost of SAX; -R$ 131,130 in 3 years).

Discussion

DPP-4 inhibitors such as SAX are new therapies with proven efficacy as adjuncts to MF for patients who have failed to achieve the goal of HbA1c in monotherapy but new anti-hyperglycemic medications can have higher unit costs compared to previous well-established therapeutic options. More comprehensive assessments, considering total costs of treatment and expected health benefits, can help decision-makers analyze whether higher acquisition costs may be offset by higher therapeutic results, leading to future projected savings for the private health care system. Decision-making supported in economic appraisal is a reality in several countries where political guidelines and reimbursement lists are developed using cost-effectiveness results. An example is the recommendation of additional therapy with DDP-4 inhibitors for patients with poor glycemic control in the United Kingdom, supported by results also obtained from the UKPDS Outcomes Model[37,38].

A systematic review on cost-effectiveness of interventions in DM2 found strong evidence to classify the intensive glycemic control, as proposed in UKPDS, compared to conventional glycemic control as a very cost-effective strategy[39]. In other contexts DDP-4 inhibitors proved to be a cost-effective additional therapy when compared to other oral anti-hypoglycemic medications[40,41]. The addition of SAX to MF therapy in patients who did not reach the HbA1c goal proved to be a resource-saving strategy in this study. Additionally, the budget impact analysis indicated that the reimbursement of SAX would lead to significant cost savings from the perspective of a private paying source in the first three years. The BIM did not consider costs occurring from adverse events to ensure a conservative approach, since the DPP-4 class has the most favorable safety profile among all oral hypoglycemic medications[32], thus higher savings could be obtained as a result of lower costs related to adverse events. The Brazilian data regarding cost-effectiveness of interventions to treat and prevent long-term complications of DM are still scarce. Nevertheless, studies of the disease cost have become increasingly frequent, especially those dealing with the economic burden of the chronic complications of DM[14,17,19].

The association between glycemic control and occurrence of DM complications is well-established and it is believed that strategies targeting the maintenance of adequate levels of HbA1c reduce costs related to complications[15,42,43]. The simulation model used in this study was able to reproduce the long-term benefits of glycemic control by reducing the risk of MI, CHF, stroke, amputation, TSRD, and blindness. Generally, the difficulty to maintain patients with DM2 within glycemic control targets is acknowledged, as evidenced by Brazilian studies that assessed this issue[12-14]. It is known that the causes of this problem are multifactorial and include issues related to changes in lifestyle and compliance with the drug treatment. Despite the complexity of the matter, it is believed that new therapeutic strategies targeting the subgroup of patients who did not achieve control with MF alone can improve this scenario, as estimated specifically for SAX in this study.

The discrete event simulation model used in this study, named the UKPDS Outcomes Model, has significant advantages over other DM simulation models: (1) it was designed to properly assess interventions that affect risk factors with well-established association with DM2-related complications; (2) the model can be used to simulate health outcomes in populations with different baseline characteristics and risk factors[26]; (3) it used UKPDS data, which is one of the most important studies on DM already conducted and with results that are considered evidence of high level in the specialization, although it has some known limitations such as not presenting diabetic neuropathy as one of the assessed complications[15]. In addition, the main source of data related to costs was an observational study that investigated the specific context of patients treated in the private health care system in Brazil (DIAPS79)[27].

Some limitations of the model should be mentioned. Not all the DM complications are included in the model and it was assumed that the negative impact on the quality of life is caused only by complications (neither the progression of disease severity itself nor the therapeutic strategies are linked to decreases of utility in the model). Additionally, the utility values were obtained from other countries due to lack of local data. New studies are needed to obtain utility data and additional economic analyses, and this could broaden knowledge about the impacts of new therapeutic strategies for the control of blood glucose, supporting multi-criteria decision-making analysis in Brazil.

Conclusion

From the perspective of private paying source, it is projected that that adding SAX to MF saves costs when compared to the addition of ROS or PIO in patients with DM2 that have not reached the HbA1c objective with MF monotherapy. The BIM of SAX inclusion in the reimbursement lists of health plans indicated significant savings within the three-year horizon.

References

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21(9):1414-31.
2. Barceló A, Rajpathak S. Incidence and prevalence of diabetes mellitus in the Americas. Rev Panam Salud Pública. 2001;10(5):300-8.
3. Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. Nat Med. 2006;12(1):62-6.
4. Bosi PL, Carvalho AM, Contrera D, Casale G, Pereira MA, Gronner MF, et al. Prevalência de diabetes melito e tolerância à glicose diminuída na população urbana de 30 a 79 anos da cidade de São Carlos, São Paulo. Arq Bras Endocrinol Metab. 2009;53(6):726-732.
5. Costa JSD, Olinto MTA, Assunção MCF, Gigante DP, Macedo S, Menezes AMB. Prevalence of diabetes mellitus in southern Brazil : a population-based study. Rev Saúde Pública. 2006;40(3):542-5.
6. Schaan BDA, Harzheim E, Gus I. Cardiac risk profile in diabetes mellitus and impaired fasting glucose. Rev Saúde Pública. 2004;38(4):529-36.
7. Torquato MTDCG, Montenegro Junior RM, Viana LAL, Souza RAHGD, Lanna CMM, Lucas JCB, et al. Prevalence of diabetes mellitus and impaired glucose tolerance in the urban population aged 30-69 years in Ribeirão Preto (São Paulo), Brazil. São Paulo Med J. 2003;121(6):224-30.
8. Malerbi DA, Franco LJ. Multicenter study of the prevalence of diabetes mellitus and impaired glucose tolerance in the urban Brazilian population aged 30-69 yr. The Brazilian Cooperative Group on the Study of Diabetes Prevalence. Diabetes Care. 1992;15(11):1509-16.
9. Schaan BD, Harzheim E, Gus I. Cardiac risk profile in diabetes mellitus and impaired fasting glucose. Rev Saúde Pública. 2004;38(4):529-36.
10. Oliveira AF, Valente JG, Leite IDC, Shcramm JMDA, Azevedo ASR, Gadelha AMJ. Global burden of disease attributable to diabetes mellitus in Brazil. Cad Saúde Pública. 2009;25(6):1234-44.
11. World Health Organization. The World Health Report 2002: reducing risks, promoting healthy life. Geneva. 2002. Available from: http://www.who.int/whr/2002/en/whr02_en.pdf.
12. Panarotto D, Salibe M, Oliveira D, Teles AR. Controle glicêmico de pacientes diabéticos tipo 2 nos serviços público e privado de Saúde. Arq Bras Endocrinol Metab. 2009;53(6):733-40.
13. Mendes ABV, Fittipaldi JAS, Neves RCS, Chacra AR, Moreira ED. Prevalence and correlates of inadequate glycaemic control: results from a nationwide survey in 6,671 adults with diabetes in Brazil. Acta Diabetologica. 2010;47(2):137-45.
14. Gomes MDB, Gianella D, Faria M, Tambascia M, Fonseca RM, Réa R, et al. Prevalence of type 2 diabetic patients within the targets of care guidelines in daily clinical practice: a multi-center study in Brazil. Rev Diabet Stud. 2006;3(2):73-8.
15. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.
16. Gerich J. The importance of tight glycemic control. Am J Med. 2005;118 (Suppl 9A):7S-11S.
17. Chaves L, Anselmi M, Barbeira C, Hayashida M. Estudo da sobrevida de pacientes submetidos a hemodiálise e estimativa de gastos no município de Ribeirão Preto-SP. Rev Esc Enferm USP. 2002;36(2):193-9.
18. Milman MHSA, Leme CBM, Borelli DT, Kater FR, Baccili ECDC, Rocha RCM, et al. Pé diabético: avaliação da evolução e custo hospitalar de pacientes internados no Conjunto Hospitalar de Sorocaba. Arq Bras Endocrinol Metab. 2001;45(5):447-51.
19. Rezende KF, Nunes MAP, Melo NH, Malerbi D, Chacra AR, Ferraz M. Internações por pé diabético: comparação entre o custo direto estimado e o desembolso do SUS. Arq Bras Endocrinol Metab. 2008;52(3):523-30.
20. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Res Opin. 2009;25(10):2401-11.
21. Rosenstock J, Sankoh S, List J. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. Diabetes Obes Metab. 2008;10(5):376-86.
22. DeFronzo RA, Hissa MN, Garber AJ, Luiz Gross J, Yuyan Duan R, Ravichandran S, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care. 2009;32(9):1649-55.
23. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab. 2009;11(6):611-22.
24. Nita ME, Secoli SR, Nobre M, Ono-Nita S. Health technology assessment: research methodology. Arq Gastroenterol. 2009;46(4):252-6.
25. Nita ME, Secoli SR, Nobre M, Ono-Nita SK, Campino ACC, Sarti FM, et al. Avaliação de tecnologias em saúde: evidência clínica, análise econômica e análise de decisão. Porto Alegre: Artmed; 2010.
26. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom prospective diabetes study (UKPDS) outcomes model (UKPDS no. 68). Diabetologia. 2004;47(10):1747-59.
27. DIAPS 79 Study Group; Eliaschewitz FG, Bahia L, Cintra M, Franco L, Nita ME, et al. Treatment patterns and achievement of therapeutic goals in a cohort of type 2 diabetes mellitus patients treated in the brazilian private health care system (PHCS): initial reports of DIAPS 79 study. Value Health. 2010;13(7):A301.
28. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, Vähätalo M, Virtamo H, Nikkilä K et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia. 2006;49(3):442-51.
29. Polonsky T, Mazzone T, Davidson M. The clinical implications of the CHICAGO study for the management of cardiovascular risk in patients with type 2 diabetes mellitus. Trends Cardiovasc Med. 2009;19(3):94-9.
30. tewart MW, Cirkel DT, Furuseth K, Donaldson J, Biswas N, Starkie MG, et al. Effect of metformin plus roziglitazone compared with metformin alone on glycaemic control in well-controlled Type 2 diabetes. Diabet Med. 2006;23(10):1069-78.
31. Mwamburi M, Xu Y, Fahrbach K. A systematic review and meta-analysis of clinical efficacy and safety of mixed treatments for type 2 diabetes Mellitus. Lexington, MA: United BioSource Corporation; 2009.

32. Phung OJ, Scholle JM, Talwar M, Coleman C. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA. 2010;303(14):1410-8.
33. Department of Health (England). Health survey for England. Department of Health; 2010. [cited 2011 Nov 22]. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/PublishedSurvey/HealthSurveyForEngland/Healthsurveyresults/index.htm.
34. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making. 2002;22(4):340-9.
35. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006;22(8):1523-34.
36. Belon AP, Maria P, Bergamo S, Berti M, Barros DA, Luis C, et al. Diabetes em idosos: perfil sócio-demográfico e uso de serviços de saúde. In: XVI Encontro Nacional de Estudos Populacionais, ABEP Caxambu-MG 2008 set/out 29-03. Belo Horizonte: ABEP; 2008.
37. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technol Assess. 2010;14(36):1-248.
38. National Institute for Health and Clinical Excellence. Newer agents for blood glucose control in type 2 diabetes. NICE Short Clinical Guidance 2009;87:1-102.
39. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010;33(8):1872-94.
40. Schwarz B, Gouveia M, Chen J, Nocea G, Jameson K, Cook J, et al. 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. 2008;10(Suppl 1):143-55.
41. McEwan P, Evans M, Bergenheim K. A population model evaluating the costs and benefits associated with different oral treatment strategies in people with type 2 diabetes. Diabetes Obes Metab. 2010;12(7):623-30.
42. Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J. 2006;152(1):27-38.
43. Adler AI, Erqou S, Lima TA, Robinson A. Association between glycated haemoglobin and the risk of lower extremity amputation in patients with diabetes mellitus-review and meta-analysis. Diabetologia. 2010;53(5):840-9.