Biological Forum – An International Journal **11(2): 107-112(2019)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Cost–Effectiveness Analysis of Vildagliptin versus Sulfonylurea Associated with Metformin in the Second-Line Pharmacotherapy of Type 2 Diabetes Mellitus: A Systematic Review

Nguyen Thi Thu Thuy[1], Pham Thi Thuy Linh[2], Nguyen Chau Ai[1], Nguyen Tran Trung[1] and Nguyen Minh Quan

[1]Pharmacy Faculty, University of Medicine and Pharmacy at Ho Chi Minh city, Vietnam.
[2]Hospital of Thu Duc district, Ho Chi Minh city, Vietnam.

(Corresponding author: Nguyen Thi Thu Thuy)
(Received 07 April 2019, Accepted 01 July 2019)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: T2DM is the one form prevails the most of the disease, accounting for nearly 90% of all cases worldwide. Metformin monotherapy is in high recommendation as first-line pharmacotherapy and higher number of options for second-line therapy has made a raise of uncertain situations in relation to optimal treatment pathway, especially selecting between DPP4i and sulfonylurea. This systematic review aims to make an overview of cost – effectiveness of vildagliptin and sulfonylurea combined with metformin in the second-line pharmacotherapy of T2DM. A review cycle was done by utilizing the sources of the data from Medline, Cochrane, Embase and Science direct with enough key word, abstract, published in English and full text published between January 2000 and November 2017 to identify health economic examinations that calculated the cost – effectiveness of vildagliptin (DDP4i) compared with sulfonylurea (SU) in a combination with metformin in the treatment of T2DM. The articles had critical appraisal in relation with data effectiveness, data of cost and utilized models. Costs were adjusted to 2014 using the CPI and converted to Euro using exchange rate from the World Bank databases (updated). From 209 records identified through database search, 2 studies analyzing the effectiveness of cost of DDP4i/metformin in comparison with SU/metformin in the treatment of T2DM were included. Differences in studies characteristics were found only in country, perspective and population. The study result in Portugal demonstrated that the increased effectiveness of cost ratio of the DDP4i compared with SU was less than the will to make payment for threshold (€ 9,072 versus € 30,000; respectively), so DDP4i was effective of cost. This result was similar to that of Greece when concluded that DDP4i/metformin was dominant regimen in a comparison with SU/ metformin because of lower cost and higher effectiveness. This study demonstrated that DDP4i combined with metformin was a cost-effective treatment option compared with SU for the T2DM patients who are under inadequate control of metformin monotherapy.

Keywords: Type 2 diabetes mellitus, cost-effectiveness, metformin, vildagliptin, sulfonylurea.

How to cite this article: Thuy, N.T.T., Linh, P.T.T., Ai, N.C., Trung, N.T. & Quan, N.M. (2019). Cost–Effectiveness Analysis of Vildagliptin versus Sulfonylurea Associated with Metformin in the Second-Line Pharmacotherapy of Type 2 Diabetes Mellitus: A Systematic Review. *Biological Forum -An International Journal*, **11**(2): 107-112.

INTRODUCTION

Diabetes is among the most common chronic illnesses worldwide, with Type 2 diabetes mellitus (T2DM) accounting for approximately 90% of all cases. Type 2 diabetes is progressive and is characterized by increased insulin resistance, generally associated with obesity, and deteriorating b-cell function, resulting in chronic hyperglycemia. As the disease progresses, so do the micro- and macrovascular complications associated with it, which have a negative impact on the quality of life of patients and pose a huge economic burden to the health system. Current treatment recommendations advocate the use of lifestyle interventions in conjunction with metformin as first-line therapy and a series of therapeutic escalations ending with insulin injections. In the event that patients remain poorly controlled with metformin monotherapy, a second oral agent is usually added. Sulfonylureas are commonly prescribed as second-line agents, although these are associated with inherent shortcomings such as weight gain and an increased risk of hypoglycaemia. Vildagliptin (DPP-4 inhibitor) has been approved for use in patients with T2DM within the European Union (EU) since 2008. The safety and efficacy of vildagliptin, either as mono-therapy or in combination with metformin, has been established in multiple studies (Wu *et al.* 2016; Montilla *et al.*, 2014; Du *et al*., 2014; Odawara *et al*., 2014; Yavropoulou *et al*., 2015; Lukashevich *et al*., 2014; Shete *et al.*, 2013; Khattab *et al*., 2016; Bosi, *et al.*, 2009; Matthews *et al.*, 2010; Bolli *et al.*, 2009; Ferrannini *et al*., 2009). There is a systematic review of cost-effectiveness of vildagliptin and other mono-therapy or combination treatment for people with type 2 diabetes mellitus in Brazil, India and Egypt (De Oliveira *et al*., 2017).

However, that review was only in Brazil, not widely available worldwide and did not specifically review cost-effectiveness of vildagliptin compare with sulfonylurea. Therefore, the objective of our systematic review is to review global studies on the cost-effectiveness of vildagliptin plus metformin compare with sulfonylurea plus metformin in treatment of type 2 diabetes mellitus.

METHODS

PRISMA guidelines were used in this review.

A. Eligibility Criteria

There was a consideration of these studies for this analysis if they (1) involved in T2DM patients; (2) included regimens of Vildagliptin/Metformin or SU/Metformin in the treatment; (3) used cost-effectiveness ratios as a outcome; and (4) used models to evaluate cost-effectiveness. Only full-text studies written in Vietnamese or English were chosen. Duplicated studies, studies not containing economic information or not mentioning vildagliptin/metformin and SU/metformin and studies which are systematic review were excluded.

B. Search strategy and study selection

We searched in databases including Pubmed, Cochrane, and Science direct to identify articles published from January 2000 to November 2017 with search term as following ("cost benefit" OR "cost-benefit" OR "Cost effective" OR "Cost-effective" OR "Cost-effectiveness" OR "Cost effectiveness" OR "cost utility" OR "cost-utility") and "Vildagliptin". After searching, publications were excluded duplicates and screened by 2 reviewers on the basis of their titles and abstracts.

C. Data extraction and summary

The articles that met the criteria were extracted information in a table. Study characteristics (year, author, country), study design (perspective, population, time horizon, cycle length, type of model, currency and index year, discount rate, sensitive analysis) and study results (costs, effectiveness, incremental cost-effectiveness ratios (ICERs), incremental cost-utility ratios (ICURs)) were objects to be recorded. The costs' results were in put in records in the currency of all the countries. Studies having current different that Euro, World Bank changed them into Euro. In every single study the cost of year when assessed was considered as 2014 by utilizing inflation rate in the country that was corresponding, said the data that the World Bank gave containing reconciled index of consumer price.

RESULTS

A. Systematic literature research

The initial search with search term on Pubmed, Cochrane and Science direct database yielded 209 potential articles, after 196 articles not containing economic information or not mentioning Vildagliptin/Metformin and SU/Metformin and 1 duplicate were remove, there were 12 articles remained. Following the full-text articles, having completed excluding 9 no full-text articles and 1 article which was systematic feedback, the articles were lessened to two, t and they moved on to undergo review containing text which was full while the selection criteria was being considered, however they still remained. Flowchart is provided in Fig. 1.

Access quality of the studies included

We conducted a qualitative assessment of the selected articles on the CHEERS scale (Yavropoulou, *et al.,* 2015) with the following assumptions:

- Achieving more than 80% of the criteria: high quality articles and remained to review.
- Achieving 50-80% of the criteria: medium quality articles and remained to review.

Achieving less than 50% of the criteria: low quality articles, excluded.

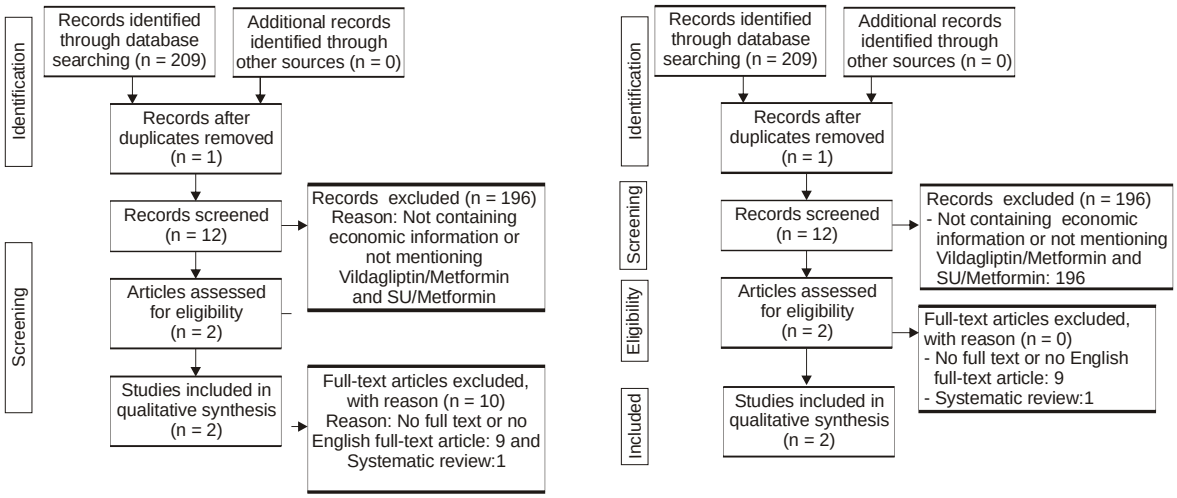

Fig. 1. Flow chart of literature research.

Table 1: Results of Cheers scale checklist.
(Kousoulakou *et al.,* 2017)(Greece) = 20/24 = 83.3%
(Viriato *et al*., 2014) (Portugal) = 21/24 = 21/24 = 87.5%

Section/item	Item	Recommendation	Reported on Page No/line No	
	No		(Kousoulakou *et al.,* 2017) (Greece)	(Viriato *et al*., 2014) (Portugal)
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	X	X
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	X	X
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study.	X	X
		Present the study question and its relevance for health policy or practice decisions.		
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	X	X
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.		
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	X	X
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	X	X
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	X	X
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	X	X
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	X	X
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	X	X
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.		
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.		X
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	X	X
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	X	X

Continue…

Section/item	Item	Recommendation	Reported on Page No/line No	
	No		(Kousoulakou *et al.*, 2017) (Greece)	(Viriato *et al*., 2014) (Portugal)
Methods				
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	X	X
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	X	X
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	X	X
Results				
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	X	X
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	X	X
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).		
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.		
Characterizing heterogeneity	19	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	X	X
Discussion				
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.		X
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.		X
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	X	

Both two articles achieved more than 80% of the criteria following CHEERS scale. Therefore, two studies were high quality articles and remained to review.

B. Study characteristics

The included articles' traits are in Table 1. In 2 studies, published in 2014 and 2017, health economic evaluations for 2 separate countries occurred: Greece, Portugal. In all 2 studies, the authors that started societal and healthcare provider perspective was applied. In all 2 studies, the study population was T2DM patients controlled in an inadequate manner on metformin.

There were the discount rates at between 0% and 8% in all 2 studies. The time horizons in all studies were different, at 40 years and a lifetime. The modelling approach which all studies used was simulation model based on the risk equations from the UK Prospective Diabetes Study Outcomes model. In addition, all studies had the similar cycle length, at 1 year. The currency used in 2 studies was the same (Euro) and the cost base year in all studies was 2014.

All of study characteristics are presented in Table 1. This table summarizes the recommended methods and modelling features of the included studies.

Table 2: Study characteristic.

Study	Country	Perspective	Study population subgroups analysed	Model	Cycle length	Time horizon	Currency (year)	Discount rate
(Kousoulakou *et al.,* 2017)	Greece	The Social Insurance Fund.	Patients who failed to achieve glycemic control with metformin mono-therapy	A cost-effectiveness patient simulation model based on the risk equations from the UK Prospective Diabetes Study Outcomes model	1 year	Lifetime	€ (2014)	between 0 and 8%
(Viriato *et al*., 2014)	Portugal	Portuguese healthcare system	Patients who failed to achieve glycemic control with metformin mono-therapy	Patient-level simulation model, utilizing the risk equations from the UK Prospective Diabetes Study Outcomes Model	1 year	40 years	€ (2014)	0% - 8%.

Table 1: Results of cost-effectiveness analyses of Vildagliptin + metformin in treatment of T2DM.

Study	Population	Intervention (weeks)	Comparator (weeks)	ICER/ICUR	Cost effectiveness
(Kousoulakou *et al.,* 2017)	10,000 patients who failed to achieve glycemic control with metformin monotherapy	Metformin + Vildagliptin	Metformin + Glimepiride	Dominant	x
(Viriato *et al*., 2014)	Patients who failed to achieve glycemic control with metformin monotherapy	Metformin + Vildagliptin	Metformin + Sulfonylurea	€ 9,072 (2014)	x

C. Study Result

For long-term effectiveness outcomes, both 2 studies reported QALYs. For cost-related outcomes, all of included studies reported costs and ICERs (Table 2). The results from cost-effectiveness analyses in treatment of patients with severe T2DM are presented in Table 2. All studies were conducted on both Vildagliptin + metfotmin and SU + metformin therapy.

According to Table 2, it is shown that Vildagliptin + metformin appeared to be dominant in comparison with SU + metformin in study of (Kousoulakou *et al.,* 2017) because of both lower cost and higher effectiveness. Beside, study of (Viriato *et al*., 2014) demonstrated that Vildagliptin + metformin is cost-effectiveness compare with SU + metformin due to ICER for metformin plus vildagliptin compared with metformin plus sulfonylurea was lower than the willingness-to-pay threshold of € 30,000 per QALY.

DISCUSSION

This systematic review aimed to compare cost–effectiveness of vildagliptin and SU add to metformin as second line pharmacotherapy of T2DM. Our systematic search identified 2 studies that assess the cost effectiveness of some medicines as second-line therapy when used in combination with metformin after failure of mono-therapy treatment with metformin in patients with T2DM. Results of studies were influenced by countries, populations, interventions and research time.

The results of our systematic review show that Vildagliptin in combination with metformin was more cost-effective compared with sulfonylurea in patients with T2DM.

Our review has a number of limitations mainly due to the number of pharmacoeconomics studies related to Vildagliptin is still very few now and there were just 2 studies in 2 countries was included. Therefore, it was difficult to conduct an overview of cost-effectiveness of Vildagliptin all over the world. The 2 included studies still have some limitations that could affect the results' quality such as the UKPDS Outcomes Model 22 in study of didn't explicitly model second events within any event categories (Viriato, *et al*., 2014); in study of patient demographics did not reflect the Greek diabetic patient population, only direct costs were considered in the analysis, reflecting only partly the economic burden of the disease, the analysis did not incorporate a number of diabetes-related comorbidities, such as peripheral neuropathy, ulceration and blindness, which are expected to impact significantly the total burden of the disease (Kousoulakou *et al.,* 2017). However, the result of our review is similar to the result of a systematic review in Brazil about cost-effectiveness of Vildagliptin compare with other hypoglycemic agent with the higher cost-effectiveness of Vildagliptin than other agent in treatment of T2DM (De Oliveira *et al.,* 2017).

CONCLUSION

This study demonstrated that Vildagliptin inhibitor when combined with metformin appeared as a treatment option that had effectiveness of cost in comparison to sulfonylurea for individuals with T2DM having a control of inadequacy on metformin mono-therapy. Finally, the study concluded that Vildagliptin combined with metformin is a more impactful treatment, but with a considerable cost.

REFERENCES

Bolli, G., Dotta, F., Colin, L., Minic, B., and Goodman, M. (2009). Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes, Obesity and Metabolism*, **11**(6): 589-595.

Bosi, E., Dotta, F., Jia, Y., and Goodman, M. (2009). Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*, **11**(5): 506-515.

Du, Y.F., Ou, H.Y., Beverly, E.A., and Chiu, C.J. (2014). Achieving glycemic control in elderly patients with type 2 diabetes: a critical comparison of current options. *Clinical interventions in aging*, **9**: 1963-1980.

De Oliveira, G.L.A., Guerra Júnior, A.A., Godman, B. and Acurcio, F.D.A. (2017). Cost-effectiveness of vildagliptin for people with type 2 diabetes mellitus in Brazil; findings and implications. *Expert review of pharmacoeconomics & outcomes research*, **17**(2): 109-119.

Ferrannini, E., Fonseca, V., Zinman, B., Matthews, D., Ahrén, B., Byiers, S., Shao, Q., and Dejager, S. (2009). Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. *Diabetes, Obesity and Metabolism*, **11**(2): 157-166.

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., ... and ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. (2013). Consolidated health economic evaluation reporting standards (CHEERS)-explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value in Health*, **16**(2): 231-250.

Khattab, M., Mahmoud, K., and Shaltout, I. (2016). Effect of vildagliptin versus sulfonylurea in muslim patients with type 2 diabetes fasting during Ramadan in Egypt: Results from VIRTUE study. *Diabetes Therapy*, **7**(3): 551-560.

Kousoulakou, H., Hatzikou, M., Baroutsou, V., and Yfantopoulos, J. (2017). Cost effectiveness of vildagliptin versus glimepiride as add-on treatment to metformin for the treatment of diabetes mellitus type 2 patients in Greece. *Cost Effectiveness and Resource Allocation*, **15**(1): 19.

Lukashevich, V., Del Prato, S., Araga, M., and Kothny, W. (2014). Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea. *Diabetes, Obesity and Metabolism*, **16**(5): 403-409.

Matthews, D.R., Dejager, S., Ahrén, B., Fonseca, V., Ferrannini, E., Couturier, A., Foley, J.E., and Zinman, B. (2010). Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes, Obesity and Metabolism*, **12**(9): 780-789.

Montilla, S., Marchesini, G., Sammarco, A., Trotta, M. P., Siviero, P.D., Tomino, C., Melchiorri, D. Pani, L., and Group, A. A.D.M. (2014). Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: data from the Italian AIFA Anti-diabetics Monitoring Registry. *Nutrition, Metabolism and Cardiovascular Diseases*, **24**(12): 1346-1353.

Odawara, M., Hamada, I., and Suzuki, M. (2014). Efficacy and safety of vildagliptin as add-on to metformin in Japanese patients with Type 2 diabetes mellitus. *Diabetes Therapy*, **5**(1): 169-181.

Shete, A., Shaikh, A., Nayeem, K.J., Rodrigues, L., Ali, M.S.S., Shah, P., Khanna, R., Majid, S., Rasheed, S.A., Shaikh, S., and Rahman, T. (2013). Vildagliptin vs sulfonylurea in Indian Muslim diabetes patients fasting during Ramadan. *World journal of diabetes*, **4**(6): 358-364.

Viriato, D., Calado, F., Gruenberger, J.B., Ong, S.H., Carvalho, D., Silva-Nunes, J., ... and Viana, R. (2014). Cost-effectiveness of metformin plus vildagliptin compared with metformin plus sulphonylurea for the treatment of patients with type 2 diabetes mellitus: a Portuguese healthcare system perspective. *Journal of medical economics*, **17**(7): 499-507.

Wu, T., Little, T.J., Bound, M.J., Borg, M., Zhang, X., Deacon, C.F., Horowitz , M., Jones, K.L., and Rayner, C.K. (2016). A protein preload enhances the glucose-lowering efficacy of vildagliptin in type 2 diabetes. *Diabetes Care*, **39**(4): 511-517.

Yavropoulou, M.P., Pikilidou, M., Kotsa, K., Michopoulos, A., Papakonstantinou, E., and Yovos, J. G. (2015). Efficacy and tolerability of vildagliptin as first line treatment in patients with diabetes type 2 in an outpatient setting. *Journal of Diabetes & Metabolic Disorders*, **14**(1): 68.