Journal of Food and Drug Analysis

Volume 20 | Issue 2 Article 10

2012

Economic evaluation of thiazolidinediones as add-on therapy for treatment of type 2 diabetic patients in the Taiwanese National Health Insurance System

Journal of Food and Drug Analysis, Vol. 20, No. 2, 2012, Pages 431-437 doi:10.6227/jfda.2012200201

Economic Evaluation of Thiazolidinediones as Add-on Therapy for Treatment of Type 2 Diabetic Patients in the Taiwanese National Health Insurance System

FEI-YUAN HSIAO[1]*, C. DANIEL MULLINS[2] AND WENG-FOUNG HUANG[3]

[1.] *Graduate Institute of Clinical Pharmacy College of Medicine, National Taiwan University, Taipei, Taiwan, R.O.C.*
[2.] *Pharmaceutical Health Services Department University of Maryland School of Pharmacy Baltimore, U.S.A.*
[3.] *Institute of Health and Welfare Policy, National Yang-Ming University, Taipei, Taiwan, R.O.C.*

(Received: June 21, 2011; Accepted: December 29, 2011)

ABSTRACT

The cost-effectiveness of adding the two health insurance covered thiazolidinediones (TZDs)- rosiglitazone or pioglitazone, to metformin in treating type 2 diabetes mellitus was assessed from a Taiwanese National Health Insurance (NHI) perspective.

This analysis was based on patient-level data extracted from Taiwan's NHI databases. Type 2 diabetic patients who received consecutive metformin treatments between 2001 and 2005 were identified. Clinical effectiveness, a proxy of glycemic control (time to insulin dependence), and direct medical cost were also estimated. Incremental cost-effectiveness ratio (ICER) was calculated and expressed as cost per delayed year to insulin dependence.

Compared to add-on non-TZDs, add-on rosiglitazone and pioglitazone were associated with delays of additional 151 days (0.41 years) and 101 days (0.28 years) in insulin dependence, respectively. Total mean medical costs were higher in add-on TZDs users compared to add-on non-TZDs users. The additional total medical costs of add-on rosiglitazone or pioglitazone were comparable, with ICERs of 95,874 and 95,485 New Taiwan (NT) dollars per year delay in insulin dependence, respectively.

Add-on TZDs improves glycemic control but also increases direct medical cost. In terms of the incremental medical costs associated with these clinical benefits, add-on rosiglitazone or pioglitazone are similar in Taiwan.

Key words: thiazolidinediones (TZDs), cost-effectiveness, incremental cost-effectiveness ratio (ICER), diabetes mellitus, national health insurance

INTRODUCTION

The clinical and economic consequences of type 2 diabetes mellitus, with its increasing prevalence and increased risk of macrovascular and microvascular complications, made it a significant public health issue of concern. According to the World Health Organization, the prevalence of diabetes across all age-groups worldwide was estimated at 2.8% in 2000 and predicted to be 4.4% in 2030[(1)]. Prevalence of type 2 diabetes mellitus in Taiwan is also high. The estimated national prevalence in 2001 was 3.13%. The prevalence among adults over 45 years old is of particular concern. According to the 2004 Report on Healthcare Quality in Diabetes Mellitus, the prevalence of type 2 diabetes mellitus among Taiwanese adults age 45-64 and age over 65 years old were 7.18% and 15.32%, respectively, in 2001. It is noteworthy that the prevalence gradually increased over a three-year period (prevalence in 2003, age 45-64 and over 65 years old were 7.71% and 15.32%, respectively)[(2)].

Diabetes mellitus inflicts considerable burden on both the patient and the national healthcare budget[(3)]. The cost of diabetic-related complications, especially the macrovascular (cardiovascular) complications, is the main cost driver[(4)]. It is well-established that aggressive management of hyperglycemia to maintain tight glycemic control can substantially reduce the risk of complications resulted from type 2 diabetes[(5,6)] and costs[(7,8)]. However, due to potential harmful effect of intensive insulin therapy on macrovascular events in recent literatures[(9,10)], the selection of second-step diabetic management for patients who fail to achieve their glycemic control has become a dilemma.

Both rosiglitazone and pioglitazone are members of the thiazolidinediones (TZDs) class of oral antidiabetic drugs (OAD) that improve glycemic control by reducing the body's resistance to insulin[(11)]. With this promising mechanism, TZDs offered potential benefits in type 2 diabetic patients.

* Author for correspondence. Tel: +886-02-23123456 ext.88347; E-mail: fyshsiao@ntu.edu.tw

Their use spread quickly throughout the United States, Taiwan, and other countries for the treatment of type 2 diabetes mellitus since they entered the market. According to data derived from the National Prescription Audit (NPA), the use of TZDs in the US continued to increase and peaked at 34% of total visits with a diabetic treatment in 2005 since the introduction of rosiglitazone and pioglitazone in 1999[12]. In Taiwan, the Bureau of National Health Insurance (NHI) also reported that annual prescriptions of TZDs (rosiglitazone and pioglitazone) increased from 1.42% to 10.78% of all prescriptions of antidiabetic agents for type 2 diabetes patients over a three-year period (2001-2003)[2].

However, the high price and increased utilization of TZDs among diabetic patients in Taiwan raises significant concern from a financial perspective. To enable healthcare payers to budget appropriately, estimating the cost of new treatment becomes more important as increasing costs stretch limited health care resources, especially in the Taiwanese government-run mandatory health care system. International experiences have demonstrated the value of economic evaluation for decision makers in the health care sector; however, while there were several cost-effectiveness studies in TZDs conducted in other countries[13-16], none has ever been performed in Taiwan. In addition, most of the studies derived their effectiveness data from clinical trials or meta-analyses and implemented cost data from their own countries. These results cannot be applied to other countries because of the differences in health-care system and resource utilization patterns. Therefore, the objective of our study was to conduct a cost-effectiveness analysis to evaluate TZDs (rosiglitazone or pioglitazone) as add-on therapy for treatments in type 2 diabetic patients in the NHI system in Taiwan.

MATERIALS AND METHODS

From a national health insurance system perspective, this study estimated the cost-effectiveness of adding TZDs (rosiglitazone or pioglitazone) compared to older treatments among type 2 diabetic patients already on metformin. TZDs are only indicated in Taiwan as an add-on to type 2 diabetic patients who cannot maintain their blood glucose level by conventional OAD. Therefore, our study cohorts were stratified based on whether patients received an add-on of TZDs (rosiglitazone, pioglitazone) or other non-TZDs OAD (metformin, sulfonylureas (chlorpropamide, glibornuride, gliclazide, glimepiride, gliquidone, glipizide, glyburide, tolazamide, tolbutamide, nateglinide, repaglinide, and acarbose) following treatment of metformin for at least 3 consecutive prescriptions. Patients who remained on monotherapy or used insulin directly after the metformin therapy were not included in our study cohort.

I. *Data Source*

The analysis was based on the 2000-2005 Taiwan's NHI databases. Launched in 1995, Taiwan's NHI system is a mandatory, single-payer, health insurance program organized by the government and operated by the Bureau of NHI in Taiwan. With approximately 23 million insured, it covers over 99% of the population in Taiwan.

The Bureau of NHI, Taiwan and the National Health Research Institutes (NHRI), Taiwan, maintains a database of uniquely identified claims and transactions for all covered services utilized by patients enrolled in the program. This database includes information on demographic, clinical, medical resource utilization (outpatient and inpatient visits), costs of services, and treatment patterns. The completeness and accuracy of the NHI claims databases are also ensured by the Bureau of NHI and NHRI, Taiwan[17].

II. *Study Cohort*

Patients with type 2 diabetes were identified from Taiwan's NHI claims database. The inclusion criteria reflected patients who had their first ambulatory visits with a diagnosis of diabetes mellitus (ICD-9CM codes: 250.xx) and received at least three consecutive prescriptions for metformin between 2001 and 2005. The cohort entry date (index date) for each patient was defined as the date when the oral hypoglycemic treatment was first prescribed. Patients were excluded if they had type 1 diabetes (ICD-9CM codes: 250.x1) or if they took insulin only during the study period.

III. *Effectiveness*

The clinical effectiveness measure is the time to the commencement of insulin dependence with at least three consecutive claims of insulin, which is presumed to reflect the treatment failure with OAD. According to the International Diabetes Federation guidelines[11], when glycemic target cannot be achieved with OAD alone, insulin therapy could be initiated. Insulin dependence was defined as the date of the first insulin claim when patients start receiving three consecutive insulin prescriptions. Patients who did not have events of insulin initiation were censored at the end of study period (December 31, 2005). The mean follow-up time of our study subjects were 926.68 days (2.35 years).

IV. *Costs*

The perspective taken for estimating costs was that of the Taiwan's NHI. All direct medical costs were based on the reimbursement cost and treatment practice obtained from the Taiwan's NHI system. All costs were expressed in New Taiwan (NT) dollars (currency exchange rate of June, 2011, 28 NT dollars = 1 US dollar).

Diabetic medication costs were the sum of study medication, i.e., rosiglitazone (4 mg, NHI reimbursement price: NT 39 dollars) or pioglitazone (30 mg, NHI reimbursement price: NT 59 dollars), and other hyperglycemic medications. All costs were based on the number of doses and days taken for each medication reimbursed by the NHI system in Taiwan. In addition to diabetic medication cost, direct medical costs including any cost incurred for either outpatient or inpatient

Journal of Food and Drug Analysis, Vol. 20, No. 2, 2012

services in the NHI system were calculated. Direct medical costs for claims with diabetes-specific codes were separated from other outpatient costs to estimate the cost of managing type 2 diabetes mellitus in routine clinical practice. Other outpatient costs irrelevant to type 2 diabetes mellitus were summed as a separate category, outpatient visit cost (others).

V. *Statistical Analyses*

Regression models were used to evaluate the association between the time to insulin dependence and the selection of TZDs versus other OADs as add-on therapy. All analyses controlled patient demographics (age and gender), severity of diabetes (diabetic hospitalizations), comorbidities (Charlson comorbidity index and CV diseases), other medical conditions (hypertension, hyperlipidemia and chronic kidney diseases) and physician specialty (endocrinologist). Data for severity of diabetes and comorbidities were based on participants' inpatient claims data during the 12 months prior to the index date. Other medical conditions were obtained from the outpatient claims 12 months prior to the index date.

Cost-effectiveness was expressed in terms of the incremental cost-effectiveness ratio (ICER) for the add-on TZDs arms versus add-on of non-TZDs OADs. The ICER was calculated as the additional resource consumption needed for an increase in an additional unit of effectiveness. More specifically, the ICER reports the additional cost per additional day delayed in insulin dependence for patients treated with add-on rosiglitazone or pioglitazone compared to those with add-on conventional OADs (non-TZDs).

RESULTS

I. *Patient Population*

Among 61,925 newly diagnosed type 2 diabetic patients with three consecutive metformin prescriptions, there were 24,928 patients who took combination therapy during the follow-up. Patients whose add-on drugs included both rosiglitazone and pioglitazone were excluded to avoid cross-over effect. We therefore identified 24,654 patients with type 2 diabetes mellitus who met our inclusion/exclusion criteria between 2001 and 2005. Our study cohort was further stratified based on their add-on drugs, which included 2,699 (10.95%) patients who received add-on rosiglitazone, 714 (2.90%) pioglitazone and 21,241 (86.17%) conventional (non-TZDs) OAD during the follow-up period (Figure 1).

The age and gender distribution, medical history and comorbidities between TZDs and non-TZDs users were similar (Table 1). A slightly higher proportion of those prescribed TZDs (1.82%) had a previous history of angina pectoris than those prescribed an add-on of non-TZDs (1.08%). Patients who were prescribed an add-on rosiglitazone (27.49%) or pioglitazone (26.61%) also were more likely to have a previous history of hyperlipidemia than those were prescribed an add-on of non-TZDs (24.80%). A much higher proportion of pioglitazone patients saw an endocrinologist.

II. *Effectiveness*

Based on our regression models, the use of TZDs as add-on therapy compared to non-TZD add-on therapy was associated with a delay of insulin dependence. Rosiglitazone and pioglitazone were associated with an additional 151 days ($p < 0.001$) and 101 days ($p < 0.001$) of delay, respectively, in insulin dependence. Patients who saw an endocrinologist for their diabetes mellitus management had a prolonged time to insulin dependence while those with a Charlson comorbidity index greater than 2 had a shorter time to insulin dependence. Severity of diabetes was non-significantly associated with a shorter time to insulin dependence (Table 2).

III. *Costs and Incremental Cost-Effectiveness*

Compared to patients who added non-TZDs, those who

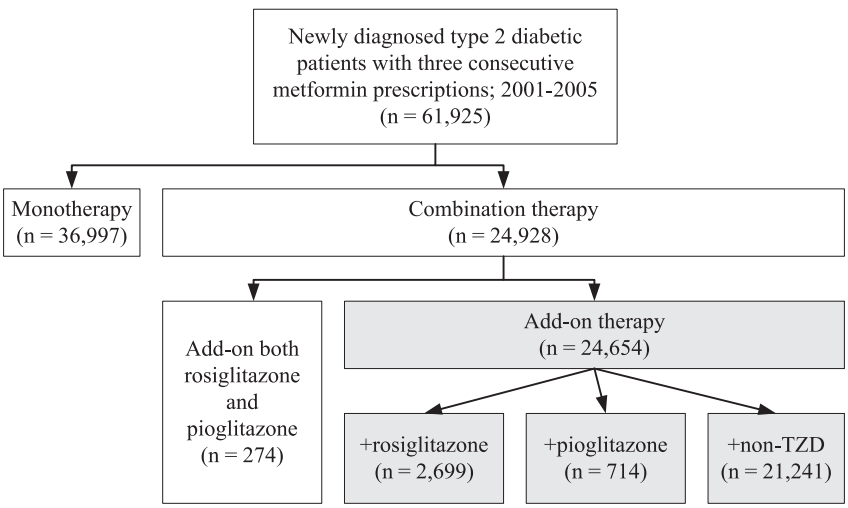

Figure 1. Flowchart of the study cohort.

Table 1. Baseline characteristics at cohort entry

	Metformin (n = 24,654)						
	+ Rosiglitazone (n = 2,699)		+ Pioglitazone (n = 714)		+ Non-TZDs (n = 21,241)		*P-value*
Characteristics	n	%	n	%	n	%	
Age, mean(SD), y	56.16	13.37	54.77	12.90	57.42	13.31	
Male	1,400	51.87	350	49.02	10,702	50.38	0.250
Prior diabetic hospital admissions	109	4.04	16	2.24	861	4.05	0.052
History of CV disease							
Composite CV events	103	3.82	26	3.64	777	3.66	0.918
Myocardial infarction	8	0.30	5	0.70	106	0.50	0.250
Congestive heart failure	6	0.22	1	0.14	78	0.37	0.307
Stroke	39	1.44	9	1.26	350	1.65	0.549
Angina pectoris	49	1.82	13	1.82	230	1.08	0.001
Transient ischemic attack	9	0.33	0	0.00	79	0.00	0.255
PTCA	18	0.67	5	0.70	108	0.51	0.464
CABG	6	0.22	2	0.28	20	0.09	0.072
Charlson comorbidity index							
2+	22	0.82	1	0.14	210	0.99	0.053
History of other medical conditions							
Hypertension	1,138	42.16	282	39.50	8,623	40.60	0.234
Hyperlipidemia	742	27.49	190	26.61	5,267	24.80	0.007
Chronic kidney diseases	20	0.74	6	0.84	116	0.55	0.289
Physician specialty							
Endocrinologist	680	25.19	286	40.06	5,464	25.72	<0.001

Abbreviations: CV = cardiovascular; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft surgery ;

Table 2. Model adjusted time to permanent insulin initiation (days)

Parameter	Parameter Estimate	Standard Error	P-value
Add on treatment dummy*			
(ref: + Non-TZDs)			
+ Rosiglitazone	151.03	9.91	<0.001
+ Pioglitazone	101.07	18.49	<0.001
Covariates**			
age (yr)	0.58	0.24	0.02
gender (male)	-29.29	6.21	<0.001
Prior diabetic hospital admissions	-21.19	19.82	0.29
Charlson comorbidity index (>= 2)	-125.71	11.21	<0.001
Endocrinologist	41.57	7.13	<0.001
Constant form	892.42	14.87	<0.001

*Compared to add-on non-TZDs, add-on rosiglitazone was associated with an additional 151 days ($p < 0.001$) and pioglitazone was associated with an additional 101days ($p < 0.001$) of delay in insulin dependence.

**Male patients were associated with a shorter time to insulin initiation (29 days shorter than female patients). Patients with a Charlson comorbidity index greater than 2 had a shorter time to insulin initiation (125 days shorter than those with less comorbidities) while those who saw an endocrinologist for their diabetes mellitus management had a prolonged time to insulin dependence (41 days longer than those who did not).

Journal of Food and Drug Analysis, Vol. 20, No. 2, 2012

Table 3. Direct medical costs during patient follow-up

	Metformin					
	+ Rosiglitazone		+ Pioglitazone		+ Non-TZDs	
Cost (per patient); NT dollars	mean	SD	mean	SD	mean	SD
Total direct costs	153,162	199,181	139,931	188,852	113,492	177,030
Treatment costs (diabetic medications)	16,895	16,967	18,697	18,419	6,183	6,692
Outpatient visit cost	89,114	103,407	85,518	123,926	65,984	81,674
Diabetes mellitus-related	24,150	38,427	23,411	28,426	16,322	22,039
Others	64,964	95,503	62,107	119,066	49,663	76,954
Hospitalization cost	47,153	142,649	35,716	102,942	41,325	136,181

*NT dollars: New Taiwan dollars, Currency exchange rate (June, 2011), 28 NT dollars = 1 US dollars.

Table 4. Incremental cost-effectiveness (add-on rosiglitazone or pioglitazone vs non-TZDs)

	Adjusted effectiveness		Total medical cost	*difference*	ICER
	(days)	(years)	(NT dollars)		
Add-on treatment					
+ Non-TZD			113,492		
+ Rosiglitazone	151.03	0.41	153,162	39,670	95,874
+ Pioglitazone	101.07	0.28	139,931	26,439	95,485

Adjusted effectiveness: delay in starting insulin treatment.
ICER: incremental cost-effectiveness ratio.
NT dollars: New Taiwan dollars, Currency exchange rate (June, 2011), 28 NT dollars = 1 US dollars.

added TZDs had higher total medical cost (NT dollars, mean; add-on rosiglitazone: 153,162, add-on pioglitazone: 139,931, add-on non-TZDs: 113,492) during the follow-up period. A breakdown of total medical cost per patient demonstrated that the major cost differences were associated with diabetic medication and outpatient visit costs. Diabetic medication costs were approximately three times as great among patients on add-on TZDs versus non-TZDs (NT dollars, mean; add-on rosiglitazone: 16,895, add-on pioglitazone: 18,697, add-on non-TZDs: 6,183) during the follow-up. Among all groups, patients who were prescribed an add-on of rosiglitazone were associated with the highest outpatient visit cost (89,114 [103,407] NT dollars) and hospitalization cost (47,153 NT dollars) (Table 3).

Using the adjusted results from the regression model and converting the estimated time to start insulin treatment from days to years, rosiglitazone and pioglitazone delayed time to insulin dependence by 0.41 and 0.28 year, respectively, compared to non-TZDs. Combining the cost and effectiveness results, the additional total medical costs of add-on rosiglitazone or pioglitazone were comparable, with the ICERs of 95,874 and 95,485 NT dollars per year delay to start insulin treatment, respectively (Table 4).

DISCUSSION

Combination use of OADs has been highly recommended for patients with suboptimal glycemic control to delay the disease progression and to reduce the long-term risks of macrovascular and microvascular complications[18]. The current study in type 2 diabetic patients showed that the add-on of TZDs, compared to that of non-TZDs, was associated with a delay in insulin dependence. At the same time, adding TZDs resulted in higher medical costs. Our empirical findings on glycemic effect are in line with previous findings with combination use of rosiglitazone[19] or pioglitazone plus metformin[20]. Furthermore, our study presented additional clinical benefits by comparing the add-on of TZDs and non-TZDs, which would provide more evidence in selecting the add-on agents when the monotherapy fail to maintain glycemic control over time.

Insulin is one of the second steps among the stepwise strategies to manage type 2 diabetes. Other steps after patients who failed their life style modification and metformin included add-on another oral hypoglycemic agents (such as sulfonylurea or TZD)[21]. Most type 2 diabetic patients will ultimately become insulin-dependent because of disease progression or the failure of OADs use to maintain glycemic control. Although insulin might be the most effective agent in maintaining blood glucose, only few insulin-treated patients achieve glycemic goals due to poor compliance[22,23]. Findings from the UK Prospective Diabetes Study (UKPDS) have indicated that 27% of patients prescribed insulin refused treatment[22]. Results from another study have suggested that adherence to insulin therapy among patients with type

2 diabetes was approximately 60%[23]. Numerous factors are likely to contribute to patient reluctance, the main driving force behind poor compliance to insulin treatment. Studies have shown that patients may equate insulin initiation with worsening diabetes, with their own personal failure to manage their disease, or with concern about needles or injections in public, the potential complexity of insulin regimens, hypoglycemia, or weight gain[24,25].

The launch of rosiglitazone and pioglitazone expanded the treatment options of OADs combination therapy in type 2 diabetic patients. Based on the results of a large, systematic meta-analysis, the two thiazolidinediones appear to have similar effects on glycemic control and similar side-effect profiles[26]. However, from the policy-maker's perspective, it is important to distinguish these two agents in terms of medical resource utilization. Previous studies from the perspective of the UK payer system[27] and US payer system[28] have indicated that pioglitazone plus metformin represented a dominant treatment strategy compared to rosiglitazone plus metformin over the lifetime of simulated type 2 diabetic patients and the moderately lower medical costs were largely due to reduced cardiovascular complications. Our study found that the additional total medical costs of add-on rosiglitazone (NT 95,874) or pioglitazone (NT 95,485) were similar. However, in light of a public meeting held in July 2010 by the US Food and Drug Administration (FDA) to discuss risks and benefits of rosiglitazone, it is noteworthy that add-on pioglitazone was slightly dominant in terms of cost-effectiveness in our study.

This study has several potential limitations. First, our clinical effectiveness measure is based on the time to insulin dependence, rather than life years gained or quality-adjusted life years (QALYs) gained. However, we believed that the delay of time to insulin dependence is still a good surrogate for QALYs in type 2 diabetic patients because glycemic control is a top priority for this patient population and patients prefer to avoid using insulin because of many reasons. We acknowledged that patients' attitude may play an important role in insulin initiation. However, we were unable to capture this because of our retrospective observational study design. In addition, our multivariable linear regression may not fit the outcome very well since we can only obtain our predictor variables (such as patients' comorbidities) from the claim-based database. A second limitation is that we did not calculate macrovascular event rates in our study; however, we did include medical cost for management diabetic complications, including macrovascular events in our cost analysis.

CONCLUSIONS

Based on our study, TZDs as add-on to existing diabetic treatment was associated with delayed time to insulin dependence. In terms of the incremental medical costs associated with these clinical benefits, add-on rosiglitazone and pioglitazone are similar in the NHI system in Taiwan, with a slightly more favorable profile for pioglitazone.

ACKNOWLEDGMENTS

Dr. Hsiao was supported by Taiwan's National Science Council Postdoctoral Fellowship Grant NSC-096-2917-I-564-106. This work was also supported by a research grant NSC96-2628-B-010-005-MY2 from Taiwan's National Science Council. Professor Mullins received grant support and consulting incoming from Bayer, Lilly, Novartis, Pfizer, Sanofi-Aventis. Professor Mullins also received grant support for another postdoctoral fellowship program from Takeda Pharmaceuticals. No funding was received for the design, analysis, or write-up of this study. Dr. Huang and Dr. Hsiao had no conflict of interest to declare.

We thank the Bureau of National Health Insurance (BNHI) and National Health Research Institutes (NHRI) for making the databases available for this study. The contents of this article, however, in no way represent any official position of the BNHI or NHRI. The authors bear all responsibilities for the results and the interpretation of the results. We would also like to thank Dr. Yi-Wen Tsai for providing consultation and assistance with the manuscript.

REFERENCES

1. Wild, S., Roglic, G., Green, A., Sicree, R. and King, H. 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 27: 1047-1053.
2. Report on Healthcare Quality in Diabetes Mellitus. Bureau of National Health Insurance in Taiwan. Available at: http://www.nhi.gov.tw/webdata/webdata.asp?menu=1&menu_id=7&webdata_id=848
3. [Last accessed 15 February, 2010]
4. Diamant, M. and Heine, R. J. 2003. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. Drugs. 63: 1373-1405.
5. UK Prospective Diabetes Study Group. 1998. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 352: 854-865.
6. Gaede, P., Vedel, P., Larsen, N., Jensen, G. V., Parving, H. H., and Pedersen, O. 2003. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N. Engl. J. Med. 348: 383-393.
7. White, J. R. 2002. Economic considerations in treating patients with type 2 diabetes mellitus. Am. J. Health. Syst. Pharm. 59 Suppl 9: S14-S17.
8. Wagner, E. H., Sandhu, N., Newton, K. M., McCulloch, D. K., Ramsey, S. D., and Grothaus, L. C. 2000. Effect of improved glycemic control on health-care costs and utilization. JAMA. 285: 182-189.
9. Clarke, P. M., Gray, A. M., Briggs, A., Stevens, R. J., Matthews, D. R. and Holman, R. R. UKPDS 72 United Kingdom Prospective Diabetes Study. 2005. Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). Diabetologia

48: 868-877.
10. Aas, A. M., Ohrvik, J., Malmberg, K., Rydén, L. and Birkeland, K. I. DIGAMI 2 Investigators. 2009. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. Diabetes Obes. Metab. 11: 323-329.
11. Margolis, D. J., Hoffstad, O. and Strom, B. L. 2008. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. Pharmacoepidemiol. Drug Saf. 17: 753-759.
12. European Diabetes Policy Group 1999. 1999. A desktop guide to Type 2 diabetes mellitus. Diabet. Med. 16: 716-730.
13. Alexander, G. C., Sehgal, N. L., Moloney, R. M. and Stafford, R. S. 2008. National trends in treatment of type 2 diabetes mellitus, 1994-2007. Arch. Intern. Med. 168: 2088-2094.
14. Neeser, K., Lübben, G., Siebert, U. and Schramm, W. 2004. Cost effectiveness of combination therapy with pioglitazone for type 2 diabetes mellitus from a German statutory healthcare perspective. Pharmacoeconomics. 22: 321-341.
15. Henriksson, F. 2002. Applications of economic models in healthcare: the introduction of pioglitazone in Sweden. Pharmacoeconomics. 20 Suppl: 143-53.
16. Czoski-Murray, C., Warren, E., Chilcott, J., Beverley, C., Psyllaki, M. A. and Cowan, J. 2004. Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation. Health Technol. Assess. 8: 1-91.
17. Chirakup, S., Chaiyakunapruk, N., Chaikledkeaw, U., Pongcharoensuk, P., Ongphiphadhanakul, B., Roze, S., Valentine, W. J. and Palmer, A. J. 2008. Cost-effectiveness analysis of thiazolidinediones in uncontrolled type 2 diabetic patients receiving sulfonylureas and metformin in Thailand. Value Health. 11 Suppl 1: S43-51.
18. National Health Insurance in Taiwan, 2007. Bureau of National Health Insurance. Available at: http://www.nhi.gov.tw/english/index.asp [Last accessed 15 February, 2011]
19. Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R. and Neil, H. A. 2008. 10-year follow-up of intensive glucose control in type 2 diabetes. N. Engl. J. Med. 359: 1577-1589.
20. Rosenstock, J., Rood, J., Cobitz, A., Biswas, N., Chou, H. and Garber, A. 2006. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes. Metab. 8: 650-660.
21. Perez, A., Zhao, Z., Jacks, R. and Spanheimer, R. 2009. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr. Med. Res. Opin. 25: 2915-2923.
22. Nathan, D. M., Buse, J. B., Davidson, M. B., Heine, R. J., Holman, R. R., Sherwin, R. and Zinman, B. 2006. Professional Practice Committee, American Diabetes Association; European Association for the Study of Diabetes. Diabetologia. 49: 1711-1721.
23. Rakel, R. E. 2009. Improving patient acceptance and adherence in diabetes management: a focus on insulin therapy. Adv. Ther. 26: 838-846.
24. Oliveria, S. A., Menditto, L. A., Ulcickas Yood, M., Koo, Y. H., Wells, K. E. and McCarthy, B. D. 2007. Barriers to the initiation of, and persistence with, insulin therapy. Curr. Med. Res. Opin. 23: 3105-3112.
25. Biderman, A., Noff, E., Harris, S. B., Friedman, N. and Levy, A. 2009. Treatment satisfaction of diabetic patients: what are the contributing factors? Fam. Pract. 26: 102-108.
26. Kuritzky, L. 2009. Overcoming barriers to insulin replacement. J. Fam. Pract. 58: 25 -31.
27. Norris, S. L., Carson, S. and Roberts, C. 2007. Comparative effectiveness of pioglitazone and rosiglitazone in type 2 diabetes, prediabetes, and the metabolic syndrome: a meta-analysis. Curr. Diabetes. Rev. 3: 127-140.
28. Tilden, D. P., Mariz, S., O'Bryan-Tear, G., Bottomley, J. and Diamantopoulos, A. 2007. A lifetime modelled economic evaluation comparing pioglitazone and rosiglitazone for the treatment of type 2 diabetes mellitus in the UK. Pharmacoeconomics. 25: 39-54.
29. Charles, M. S., Minshall, M. E., Pandya, B. J., Baran, R. W. and Tunis, S. L. 2009. A cost-effectiveness analysis of pioglitazone plus metformin compared with rosiglitazone plus metformin from a third-party payer perspective in the US. Curr. Med. Res. Opin. 25: 1343-1353.