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제2형 당뇨병 환자에 대한 메트포르민-글리메피리드 병합요법과 메트포르민-피오글리타존 병합요법의 비용-효과분석

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Cost-Effectiveness Analysis of Glimepiride or Pioglitazone in Combination with Metformin in Type-2 Diabetic Patients

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배경: 당뇨병 환자에게 관상동맥심질환은 생존률, 건강 상태 유지 및 삶의 질에 주요한 영향을 미치는 합병증이며 적극적인 당뇨병 치료는 이러한 심혈관 합병증을 예방할 수 있으나 당뇨병의 적극적 치료와 관리에는 많은 비용이 소요된다. 목적: 제2형 당뇨병 환자를 대상으로 메트포르민과 글리메피리드 병합요법과 메트포르민과 피오글리타존 병합요법의 비용-효과성을 비교하고자 하였다. 연구방법: 마르코프 코호트 프로세스(Markov Cohort Process Model) 모형을 이용하여 비용-효과분석을 실시하였다. 연장된 수명 (life years gained, LYG)과 삶의 질(quality)을 보정하여 증가된 QALYs를 주요 효과 지표로 측정하였고, 총비용으로는 직접의료비용과, 환자와 가족의 교통비를 직접비의료비용으로 고려하였고 환자와 가족의 시간비용을 간접비용으로 포함하였다. 연구결과: 비용-효과분석 결과, 메트포르민과 글리메피리드 병합요법의 경우 총 비용은 5,962,288원, 효과는 7.94LYG, 6.43QALY이었다. 반면 메트포르민과 피오글리타존 병합요법은 총 비용 10,982,243원, 효과 8.62LYG, 6.99QALY으로, 점증적 비용-효과비(ICER)는 7,402,663원/LYG과 8,934,546원/QALY 이었다. 결론: 우리 사회의 연장된 수명(LYG)에 따른 지불의사가 700만원 이하인 경우는 메트포르민과 글리메피리드 병합요법이 비용-효과적인 대안이며 700만원 이상인 경우에는 메트포르민과 피오글리타존 병합요법이 비용-효과적인 대안이 될 수 있다.

□ Key words - Cost-Effectiveness Analysis (CEA), Cost-Effectiveness Ratio (CER), Incremental Cost-Effectiveness Ratio (ICER); Pioglitazone; Glimepiride; Metformin

In South Korea, according to the report of joint research by the Korean Diabetes Association and Health Insurance Review Agency (HIRA) in 2005,[1] the diabetes prevalence (as of 2003) was estimated to be 5.92% (n=2,860,402). The prevalence of women was greater by 1.22 times compared with men's counterpart (5.33% for men and 6.52% for women). The prevalence for the age group of 20 to 79 is estimated to be 7.7% (n=2,694,220), which ranks South Korea 13th among 30 Organization for Economic Co-operation and Development (OECD) member countries. Assuming that this prevalence trend continues it is estimated that there will be n=3,510,000 with diabetes (7.08% of the whole population) in 2010, n=4,550,000 (8.97%) in 2020, and n=5,450,000 (10.85%) in 2030.

Cardiovascular disease is the predominant cause of death in diabetic patient.[2] Studies such as Diabetes Control and Complications Trial (DCCT)[3] and United Kingdom Prospective Diabetes Study (UKPDS),[4-11]

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have shown that intensive treatment of blood glucose can reduce the incidence of microvascular and macrovascular disease. However, the conclusion of the recent Action to Control Cardiovascular risk in Diabetes (ACCORD) study[12] note an increase in mortality in type 2 diabetic patients treated intensively, while the Action in Diabetes and Vascular disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) study evidences a reduction in microvascular complications and the Veterans Affairs Diabetes Trial (VADT) study that intensive treatment has no significant effect. Large prospective epidemiologic studies in patients with diabetes have shown that higher glucose levels predict higher rates of cardiovascular disease and the risk for a cardiovascular disease event is greater at higher values of HbA1c. A recent meta-regression analysis of epidemiologic studies reported that the risk for a cardiovascular disease event was 18% greater for each 1% increase in HbA1c.[12-25]

These observations provide strong support, though certainly not proof, that lowering glucose to levels within the normal range might prevent cardiovascular disease in diabetic patients.

The purpose of this study is to compare the cost-effectiveness of two combination therapies which are recommended by diabetes treatment guideline in South Korea (metformin and glimepiride, metformin and pioglitazone) in patients with diabetes who experienced the failure of monotherapy of metformin.

METHODS

Overview

We developed a Markov Model[26-36] to simulate and evaluate the cost-effectiveness of each combination therapies in reducing CHD in patients with type 2 diabetes (Figure 1). The model designed to estimate total cost, CHD event, LYG and QALYs and to use data from the randomized clinical trails (RCTs) chosen by systematic review.[37-43] Costs are shown in KRW, year

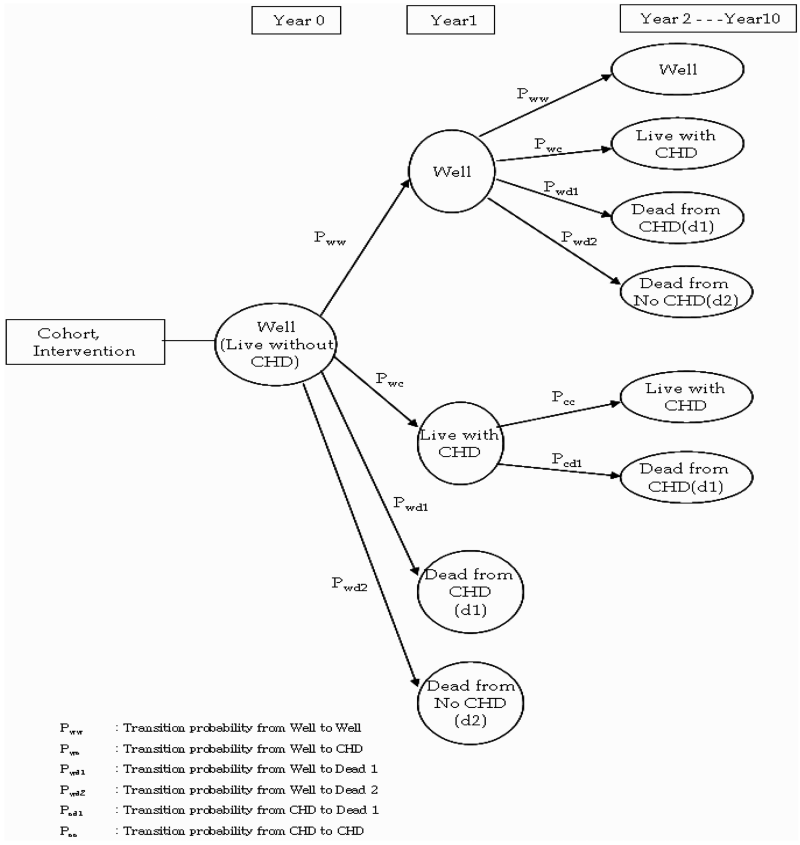

Fig. 1. The health state of Markov model and Transition probability model

2007 values. Costs and benefits were discounted at 5% per annum.

Modeling and Clinical outcomes

In view of the practice patterns in South Korea, the demographic and clinical characteristics of patients with type 2 diabetes was reflected in the model. According to the report of the Korean Diabetes Association (KDA), type 2 diabetes increased after age of 40. Considering the KDA report and the weighted average age and prevalence period of the patients in the cited clinical trials, I assumed that age of the subjects was 56 and prevalence period was 5 years. Another assumption was that all subjects who experienced the failure of monotherapy of metformin as first oral medication therapy were treated by combination therapy with metformin and glimepiride or metformin and pioglitazone.

The model is a Markov model with four mutually exclusive health states (well, live with CHD, dead from CHD, dead from no CHD) and a 1-year cycle length. A half-cycle correction was performed. Annual transition probabilities were derived from risk equations reported from UKPDS56[44] and Framingham risk engine.[45]

Input data from RCT articles are summarized in Table 1. The clinical outcome used in the analysis was calculated by extracting the intermediate effectiveness variables and the risk-factors in the incidence of CHD from the clinical trial literatures on the alternative therapy for each existing treatment, and by using disease-risk model formula.

Costs

This study adopted the societal perspective, so this study estimated direct and indirect cost related to diabetes and CHD therapy.

Direct medical cost includes drug cost, monitoring cost (medical-supplies expense, total medicine-preparation cost, medical treatment cost, examination cost), and nursing cost (charged). Direct non-medical cost includes the money spent on transportation by patients and families and indirect cost includes the time cost by patients and families.

The cost data for medications and therapy were based on the list price obtained from the formulary of the national health insurance and other costs were collected from published studies conducted under the South Korea setting.[46-52] The assumption was that all adverse events were mild and did not need special treatments,

Table 1. Input data from RCT articles used in UKPDS 56 and Framingham risk engine

Study	Drug	Study Period (week)	# of patients (M/F)	Age (year)	Sex[1]	Race[2]	Smoking[3]	HbA1c (%)	SBP (mmHg)	TC (mmol/l)	HDL-C (mmol/l)	LR[4]
Giuseppe Derosa (2005, 2006)	Met Glime	52	47 (23/24)	52±5	0/1	0	0/1	7	128.2	4.45	1.11	4.0090
Guillermo Umpierrez (2006)	Met Glime	26	96 (53/43)	51.6 ±11.8	0/1	0	0/1	7.1	128.2	4.97	1.12	4.4375
Giuseppe Derosa (2006, 2007)	Met Pio	52	48 (24/24)	55±5	0/1	0	0/1	6.8	131.3	4.53	1.24	3.6532
Guillermo Umpierrez (2006)	Met Pio	26	107 (56/51)	55.7 ±9.7	0/1	0	0/1	7.08	131.3	5.32	1.24	4.2903
D.R.Matthews (2005)	Met Pio	52	317 (161/156)	56±9.2	0/1	0	0/1	7.72	131.3	5.85	1.28	4.5703

Glime; Glimepiride, HbA1c; Hmmoglobin A1c, HDL-C; High Density Lipid Cocentration, Met; Metformin, Pio; Pioglitazone, SBP; Systolic Blood Pressure, TC; Total Cholesterol
[1]; Sex : Male 0, Female 1
[2]; Race : Afro-Caribbean 1 ; Caucasian or Asian Indian 0
[3]; Smoking : Smoking 1, Non-smoking 0
[4]; LR : TC/HDL-C

Table 2. Summary of Costs

Cost (KRW)	Met+Glime	Met+Pio
Drug cost per 1 cycle from DM[1]	183,233	730,730
The monitoring cost per 1 cycle from DM	324,095	
The direct non-medical care cost per once in an outpatient's visit to medical institution from DM	26,882	
The direct medical cost per a case in the incidence of CHD	341,598	
The direct non-medical cost according to incidence of CHD	29,196	

Met+Glime ; Metformin+Glimepiride, Met+Pio ; Metformin+Pioglitazone
[1]Daily dose : Metformin 2000 mg , Glimepiride 2 mg, Pioglitazone 30 mg
Unit drug price : Metformin 1000 mg KRW 114, Glimepiride 2 mg KRW 274, Pioglitazone 30 mg KRW 1,774

so I excluded the monitoring cost for treating adverse events of pioglitazone such as congestive heart failure. Therefore the monitoring item and frequency of the two alternative plans were the same and there was no difference in the monitoring cost. Costs are summarized in Table 2.

Analysis

The analysis was performed based upon the societal perspective and the analytic model was Markov Cohort Process Model using TreeAge Pro 2008^{TM}. 1 cycle was considered as 1 year and analysis was conducted for 10-year time horizon. Health state utilities for diabetes and CHD were 0.8250 and 0.7802 respectively (National Health and Nutrition Survey, 2005)

Sensitivity analyses were performed on key model input data to test uncertainty and to confirm the robustness of the results. Univariate analysis was conducted on key parameters which were expected to have a strong impact on the results. The varying parameters in

Table 3. Transition probability according to Markov health state

Drug	Age	Cycle	P_{ww}[1]	P_{wc}[2]	P_{wd1}[3]	P_{wd2}[4]	P_{cd1}[5]	P_{cc}[6]
Metformin+ Glimepiride	57	1	0.9068	0.0732	0.0142	0.0058	0.0505	0.9495
	58	2	0.8939	0.0825	0.0174	0.0062	0.0620	0.9380
	59	3	0.8802	0.0922	0.0210	0.0066	0.0748	0.9252
	60	4	0.8657	0.1023	0.0250	0.0071	0.0889	0.9111
	61	5	0.8503	0.1127	0.0293	0.0077	0.1043	0.8957
	62	6	0.8341	0.1234	0.0340	0.0085	0.1209	0.8791
	63	7	0.8170	0.1346	0.0390	0.0094	0.1388	0.8612
	64	8	0.7992	0.1460	0.0444	0.0105	0.1580	0.8420
	65	9	0.7803	0.1579	0.0502	0.0116	0.1786	0.8214
	66	10	0.7605	0.1704	0.0563	0.0128	0.2003	0.7997
Metformin+ Pioglitazone	57	1	0.9342	0.0516	0.0084	0.0058	0.0299	0.9701
	58	2	0.9211	0.0614	0.0113	0.0062	0.0403	0.9597
	59	3	0.9073	0.0714	0.0147	0.0066	0.0522	0.9478
	60	4	0.8927	0.0818	0.0184	0.0071	0.0657	0.9343
	61	5	0.8772	0.0925	0.0227	0.0077	0.0807	0.9193
	62	6	0.8608	0.1034	0.0273	0.0085	0.0972	0.9028
	63	7	0.8436	0.1146	0.0324	0.0094	0.1153	0.8847
	64	8	0.8255	0.1262	0.0379	0.0105	0.1349	0.8651
	65	9	0.8087	0.1359	0.0438	0.0116	0.1560	0.8440
	66	10	0.7865	0.1506	0.0502	0.0128	0.1786	0.8214

[1]P_{ww} : Transition probability from Well to Well, 1-R(t)
[2]P_{wc} : Transition probability from Well to CHD, R(t)-P_{wd}, $P_{wd} = P_{wd1} + P_{wd2}$
[3]P_{wd1}: Transition probability from Well to Dead 1, P(t)
[4]P_{wd2}: Transition probability from Well to Dead 2, Life table of general population
[5]P_{cd1}: Transition probability from CHD to Dead 1, Pwd1 X 3.56
[6]P_{cc} : Transition probability from CHD to CHD, 1-P_{cd1}

Table 4. Cost-Effectiveness and Cost-Utility analysis results

	Metformin+Glimepiride	Metformin+Pioglitazone
Cost (KRW)	5,962,288	10,982,243
LYG	7.94	8.62
QALY	6.43	6.99
CER based on CEA (KRW/LYG)	750,933	1,274,343
ICER based on CEA (KRW/LYG)		7,402,663
CER based on CUA (KRW/QALY)	927,766	1,571,505
ICER based on CUA (KRW/QALY)		8,934,546

the analyses included discount rates of 0%, 3%, and 7%, transition probability in health state, utility in each heath state, treatment period and drug cost.

RESULTS

Base case

Simulated results yield probability of CHD mortality (denoted P(t)) using Framingham formula and probability of CHD incidence (denoted R(t)) using UKPDS56 formula and the transition probability according to Markov health state was estimated using P(t), R(t), and general life table (Table 3).

Table 4 shows total cost, life years gained (LYG), quality-adjusted life years (QALY) of each combination therapies. The discounted ICERs of metformin and pioglitazone were KRW 7,402,603/LYG and KRW 8,934,546/QALY respectively.

Sensitivity Analysis

Table 5 shows the ICER values based on LYG for the variation of each input . Although there were some differences in ICER value in accordance with the input variation, the results did not change too much from the base case analysis. In case of non-smoker and female, ICER was higher than any other variation. The reason seems to be non-smoking and female have low risk in CHD incidence potentially, so there is small effect difference in reducing CHD incidence between two alternatives. In terms of the relative cost-effectiveness with net-benefit approach which compared two combination therapies over a wide range of willingness to pay (WTP) values for a unit of clinical effect, when society is willing to pay greater than KRW 7,000,000/LYG it can be cost-effective care with metformin and pioglitazone combination, which is more expensive. However, the benefits society can get from the two possible combination therapies are equal with WTP of KRW 7,000,000/LYG.

Discussion

According to UKPDS clinical trials intensive glycemic control not only reduces HbA1c, but also reduces

Table 5. ICERs of sensitivity analyses

Input data	Variation	ICER[1] (KRW/LYG)
Discount Rate	0%	6,099,389
	3%	6,845,403
	7%	7,997,887
Transition Probability	non-smoker and female	20,105,993
	non-smoker and male	7,114,134
	smoker and female	9,623,609
	smoker and male	5,331,296
	Maximum parameter of UKPDS 56 risk engine	7,053,770
	Maximum parameter of UKPDS 56 risk engine	7,911,257
	Maximum of R(t) and P(t)[2]	9,204,400
	Minimum of R(t) and P(t)	8,769,161
Treatment period	5 years	12,175,302
	20 years	6,771,197
Pioglitazone price	KRW 247	458,698
	KRW 274	583,940
	KRW 872	3,357,815
Utility	DM 0.8 and CHD 0.8	9,253,328
	DM 0.95 and CHD 0.71	7,639,606

[1] ICER : ICER of combination therapy of metformin and glimepiride based on LYG

[2] R(t) : Probability of CHD incidence, P(t) : Probability of CHD mortality

the incidence and death in complications of CHD. So, this study was conducted to compare the cost-effectiveness of two alternatives considering not only reducing HbA1c but also reducing complications of CHD.

Cost-effectiveness acceptance can be decided according to ICER threshold or WTP of society. In this study, the cost-effective alternative could be selected depending on whether WTP exceeded KRW 7,000,000/LYG or not. In South Korea, there is no confirmed ICER threshold or WTP, so further studies must be made to confirm ICER and WTP. Despite all these, metformin and pioglitazone might be considered as a cost-effective therapy through a cost-effectiveness analysis using the ICER threshold (1-2 times of GDP per capita) determined by South Korea government. In 2007, South Korea GDP per capita, reported by International Monetary Fund, was KRW 18,103,929, so considering this metformin and pioglitazone might be cost-effective.

Using Intercontinental Marketing Services (IMS) data and DM prevalence in South Korea, the number of patients who were treated by metformin and glimepiride was estimated to be 34,633 in 2007. The study result showed that if 34,633 patients were switched to metformin and pioglitazone, KRW 170 bil. will be spent for 10 years and 23.6 life years might be gained.

The studies of Douglas Coyle *et al*. (2002)[28] and Kurt Neeser *et al*. (2004)[31] conducted cost-effectiveness analysis of pioglitazone monotherapy and combination therapy with other drugs for diabetic complications such as myocardial infarction, stroke, lower extremity amputation, nephropathy and retinopathy. Douglas Coyle *et al*. (2002) showed that ICER of pioglitazone monotherapy as first line therapy was $Can 54,000/LYG compared to metformin monotherapy, and $Can 42,000/LYG compared to glibenclamide, and $Can 27,000/LYG compared to life style, food and exercise change. Pioglitazone monotherapy could be a cost-effective alternative if it could delay the use of insulin. Kurt Neeser *et al*. (2004) conducted cost-effective analysis in UKPDS clinical trial patients. The result was that ICER of the combination therapy of pioglitazone and metformin was EURO 20,002/LYG compared to the combination therapy of sulfonylurea and metformin, and EURO 5,860/LYG compared to the combination therapy of acarbose and metformin. ICER of the combination therapy of pioglitazone and sulfonylurea was EURO 8,707/LYG compared to the combination therapy of metformin and sulfonylurea, and EURO 4,443/LYG compared to the combination therapy of acarbose and metformin. Through these results, Kurt Neeser *et al*. (2004) concluded that ICER of the combination therapy of pioglitazone and metformin and pioglitazone and sulfonylurea were in an acceptable range of the German government. Usually, the value of drugs is evaluated through safety and efficacy, but in pharmacoeconomic analysis cost-effectiveness is a factor for a drug's value and rational drug selection.

This study used the standard cost-effectiveness analysis method but it had several methodological limitations. Firstly, this study extracted CHD incidence and mortality from 3 studies published from other countries instead of using Korean clinical data, which might cause limitations in terms of inconsistency and low reliability. Secondly, UKPDS 56 and Framingham risk engine used in this study had limitations, as well. Usually disease risk engine is based on large scale epidemiology studies, but UKPDS 56 risk engine was based only on UKPDS 56 clinical trial. In spite of this limitation, UKPDS 56 risk engine had an advantage of being a type 2 diabetes specific risk calculator and included HbA1c as a variable. Unlike UKPDS 56, Framingham risk engine was designed based on a large scale epidemiology study, but it was not specific risk engine for diabetes patients. Regardless of its limitations, Framingham risk engine included diabetes as a variable and so was used in many cardiovascular risk studies. Thirdly, this study used a modeling approach. Pharmacoeconomic modeling is commonly used in health economics, but it has certain limitations that have to be considered in order to place these findings properly into context. In chronic disease, transition probability change every cycle, and usually a Markov process model is used. Markov process model has a disadvantage of making an over-estimation because it extrapo-

lates long-term data from short-term clinical trial period, making assumptions in the process. Assumptions are unavoidable and they cannot reflect actual clinical status and every patient variation in modeling.

CONCLUSION

Out of the combination therapies of metformin and glimepiride and metformin and pioglitazone, neither one of the alternative plan was absolutely dominant. Just like the base case analysis, none of the two alternative therapies were dominant in sensitivity analysis. In terms of the relative cost-effectiveness with net-benefit approach, when the willingness to pay is more than 7,000,000 KRW/LYG, the combination therapy in metformin and pioglitazone can be cost-effective and when the willingness to pay is less than 7,000,000 KRW/LYG, the combination therapy in metformin and glimepiride can be cost-effective. Consequently, the cost-effective alternative between two alternatives will be able to be selected depending on threshold in willingness to pay or ICER in our society.

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