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Original Article

Cost-effectiveness analysis of statin monotherapy regimen in outpatient management of dyslipidemia in patients with diabetes mellitus

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Abstract

Diabetes mellitus and dyslipidemia are major risk factors of coronary heart disease (CHD). Statin drugs have become the first-line drug therapy for diabetic dyslipidemia. This study evaluated the cost-effectiveness of statin monotherapy by comparing Simvastatin, Atorvastatin, Rosuvastatin, Fluvastatin and Pravastatin in diabetes patients at Phramongkutklao Hospital. Statin effectiveness and cost-effectiveness in attaining low-density lipoprotein cholesterol (LDL-C) goal was evaluated. The result showed that, of 923 eligible patients, Simvastatin had the lowest mean annualized treatment cost and was the most effective statin, as indicated by the CER and the ICER, among outpatients with diabetes compared with other statins in this study.

Keywords: statin therapies, cost-effectiveness, heart disease, diabetes mellitus, dyslipidemia.

1. Introduction

Diabetes mellitus or diabetes occurs from deficiency in the body's use of insulin due to an ineffective pancreas or an ineffective body for using insulin. There are two main type of diabetes; *type 1 or insulin-dependent or juvenile-onset diabetes,* which is found in only 5–10% of patients with diabetes and *type 2 non-insulin dependent or insulin resistance*, which is found 90–95% of patients with diabetes (World Health Organization, 2011). Which causes serious damage to many of the body's systems especially the nerves and the blood vessels, which increases the risk of heart disease and stroke (Rabintossaporn *et al.*, 2009; Thuppia *et al.*, 2009). In addition, the WHO mentioned that half the people with diabetes die due to cardiovascular disease (World Health Organization, 2011). Surprisingly, more than 80% of the burden of death from diabetes occurs in low- and middle income countries such as Thailand (Aekplakorn, 2003) where coronary heart disease (CHD) is also one of the first three causes of death among the Thai population (National Institute of Diabetes and Digestive and Kidney Diseases, 2011) and a several countries (Haruko *et al.*, 2008; Henry *et al.*, 2009).

Not only is diabetes mellitus a risk factor of CHD, but also is dyslipidemia, which is defined as a disorder of blood cholesterol by an elevation of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and a reduction of high-density lipoprotein (HDL-C). Lowering blood TC and LDL-C results in a decrease of CHD morbidity and mortality (Law *et al.*, 2003; Spratt, 2004; Kannel, 2005 and Gould *et al.*, 1998). Thus, lowering TC levels where LDL-C as the primary target leading to a reduction in the burden of cardiovascular disease seems to be an ideal strategy (National Institutes of Health, 2002; Grundy *et al.*,

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Table 1. How to calculate on the ICER

Drug	Cost (USD)	Effect (% patients achieved the goal)	C/E (USD/% patients achieved the goal)	ΔC/ΔE
Simvastatin	A1	A2	A1/A2	(A1/A2)
Atorvastatin	B1	B2	B1/B2	(B1-A1)/(B2-A2)
Rosuvastatin	C1	C2	C1/C2	(C1-B1)/(C2-B2)
Fluvastatin	D1	D2	D1/D2	(D1-C1)/(D2-C2)
Pravastatin	E1	E2	E1/E2	(E1-D1)/(E2-D2)

An economic value assessment was calculated based on provider perspective. Costs included only drug costs within a time horizon of 1 year. Drug costs are based on the retail price at Phramongkutklao Hospital in 2011. These prices are converted from Baht unit to USD by using exchange rate as of average June 2011. It was 30.528 Baht/USD.

2009). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and national guideline suggest that LDL-C levels less than 100 mg/dL for adults with diabetes is optimal (National Institutes of Health, 2002; Grundy *et al.*, 2009; Ngamukot *et al.*, 2002).

HMG-coA reductase inhibitors as the statins have become the first-line drug therapy for diabetic dyslipidemia provided by NCEP ATP III (Ngamukot *et al.*, 2002), because of the most effective drugs for lowering LDL-C levels. Statins can decrease the risk for CHD by 24% to 37% of total mortality and 22% of all causes of mortality (National Institutes of Health, 2002). Five statins Simvastatin, Atorvastatin, Rosuvastatin, Fluvastatin and Pravastatin are used alone in many hospitals in Thailand, including Phramongkutklao Hospital, a large tertiary care level military hospital and the school of medicine and the biggest military hospital in Thailand. Prescriptions of these statins were among in the top ten drug expenditures for several years, especially, Rosuvastatin and Atorvastatin, in the database of Phramongkutklao Hospital.

Because of the difference in drug prices (Table 2), the rapid increase of drug expenditures, and conflicting results in effectiveness of statins between clinical trials and usual clinical practices, it is difficult to decide which statins are the most cost-effective to be selected in the hospital formulary. Furthermore, the difference of health benefit schemes affects the access for patients to each statin type. The main medical benefit schemes in Thailand consist of Civil Servant Medical Benefit Scheme (CSMBS), Social Security Schemes (SSS) and Universal Health Coverage (UC). There were 6.5 million people of Thai population (10%) with CSMBS coverage, 11% with SSS covering and 79% with UC covering estimated in 2005 (The National Bureau of Asian Research, 2012). The benefit of CSMBS covers both essential and non-essential drugs; therefore, this scheme can be called the largest scheme in terms of expenditures and comprehensive privilege. On the other hand, SSS and UC only cover essential drugs (here, only Simvastatin). Thus, scheme types and drug prices affect the access to statin types.

There are no previous studies in Thailand comparing the cost-effectiveness of the five statins among diabetic patients. Therefore, this study was conducted to compare the cost-effectiveness of Simvastatin, Atorvastatin, Rosuvastatin, Fluvastatin and Pravastatin in evaluating cost and in achieving LDL-C goal according to NCEP ATP III guidelines among diabetic patients in usual clinical practice at the Phramongkutklao Hospital. Cost-effectiveness analysis (CEA) was used in this study because the costs and consequences of treatment can be examined. Thus, achieving the LDL-C goal followed by NCEP ATP III goal might be a better outcome measure in a CEA of statin type evaluation. The appropriate comparison between statin types is in term of the incremental cost-effectiveness ratio (ICER), which can be calculated by ΔC/ΔE for each statin type, from the least costly to the most, ordered according by cost. Also, dominance is defined as one

Table 2. The difference of drug prices from retail price at Phramongkultklao Hospital depended on statin types

Drug	Trade name and dose (mg)	Price (Baht)	Price (USD)*
Simvastatin	Zimmex®(10)	2	0.07
	Bestatin®(20)	3	0.10
	Bestatin®(40)	4.75	0.16
	Zocor®(40)	39.5	1.29
Atorvastatin	Xarator®(10)	25.5	0.84
	Lipitor®(10)	41	1.34
	Lipitor®(20)	52.25	1.71
	Lipitor®(40)	61.25	2.01
Rosuvastatin	Crestor®(10)	43.5	1.43
	Crestor®(20)	65	2.13
Fluvastatin	Lescol XL®(80)	34.5	1.13
Pravastatin	Mevalotin®(20)	26.5	0.87
	Mevalotin®(40)	44.5	1.46

*Exchange Rate = 30.528 Baht/USD as of average June 2011.

statin type dominating another if its effectiveness is higher and its costs lower. On the other hand, one statin type could be excluded and called "dominated" if its effectiveness is lower and its costs higher (Drummond *et al.*, 2005). In this study, the cost-effectiveness of statin monotherapy in the clinical practice setting comparing all of the statin drugs (Simvastatin, Atorvastatin, Rosuvastatin, Fluvastatin and Pravastatin) in diabetes patients at Phramongkutklao Hospital for assessing economic value included only drug costs and surrogate outcome (LDL-C).

2. Methods

The study population was outpatients who were diagnosed with diabetes mellitus type 1 or 2 (this study included outpatients with both diabetes types) who received the statin drug during between January 2011 and December 2011 at Phramongkutklao Hospital. Our data came from the year 2011 for predicting cost-effectiveness in the following year and in the future. This study collected retrospective data from the electronic database. Inclusion and exclusion criteria for this study were;

2.1 Inclusion criteria

1. Outpatients were diabetes mellitus type 1 or 2.
2. Outpatients with dyslipidemia underwent a laboratory test to measure LDL-C level before (basevisit) and after (endvisit) taking statin drug.
3. Outpatients needed to get drug continuously during at least 3 physician visits or 3 follow up per year (because a doctor can prescribe number of drugs for a maximum of 3 months and patients need to be measured to LDL-C level every 3-6 months when they take statin drugs following the guidelines for management of dyslipidemia).
4. Outpatients must have received statin alone for reducing hyperlipidemia disease during 2011.
5. Outpatients had serum LDL-C level at baseline $\geq$ 100 mg/dL.

2.2 Exclusion criteria

1. Outpatients who switched to another statins or received other hyperlipidemia medications (Fibrate, Ezetimibe, Bile acid sequestrants and Nicotinic acid) after using statins. There patients was excluded because the study needed to follow the outcome of the effectiveness on LDL-C level reducing with specific statin type.
2. Outpatients who discontinued statin therapy.
3. Outpatients who did not have the baseline or the final LDL-C measurement.

3. Data Collection

A retrospective study was conducted utilizing the electronic database of outpatients who were treated as outpatients in the hospital. The outpatient data were extracted from the electronic database of pharmacy records into Microsoft Access 2010 for data processing. The database consists of prescriptions from doctors made on-line from doctors' office and laboratory results recorded by medical technicians in the pharmacy department system. Pharmacy dispensing database was used to estimate the dispensed prescription for considering the statin type received and diabetic therapy, which was analyzed from anti-diabetic drug. The processing of the data collected showed that there were 15,718 subjects with reported diabetes after being extracted and there were 12,668 subjects with diabetes receiving statins as statin types were recorded in outpatient's data on the electronic database. Subjects with diabetes, who received continually statins with no switching of statin types, monitored for number of drugs and received each statin type at least 270 days, was 3,894 patients. Remaining subjects who got LDL-C level test before and after comprised 2,093 patients. Subjects that had serum LDL-C level at baseline $\geq$ 100 mg/dL accounted 923 patients. Therefore, the total study population was 923 patients. Microsoft Excel version 2010 was used for data management, analysis and calculation. IBM SPSS statistics version 20 was used to assess mean and standard deviation and statistical tests, stratified by sex, health benefit scheme, LDL-C parameter, annualized cost and therapy duration with statin type.

Chi-square test was used to assess the difference of sex and health benefit scheme among statin therapies in Table 3; likewise, chi-square test was used to assess the difference of proportion of patients achieving LDL-C goal according to NCEP ATP III among statin therapies in Table 4 because variables are categorical data and Kolmogorov-Smironov test. Therefore was used to estimate the normality assumption, showed the results as a non-normal distribution. Kruskal-Wallis H test was used to assess the difference of LDL-C parameter, annualized cost and therapy duration among statin therapies in Table 3.

Cost-effectiveness, calculations used only the drug costs because this study focused on drug prices and the surrogate outcome (LDL-C level less than 100 mg/dL according to NCEP ATP III guidelines). It was assessed among statin types based on incremental cost effectiveness that was outcome measurement. The cost-effectiveness ratio (CER) usually referred to in pharmacoeconomics is the incremental cost-effectiveness ratio (ICER), which compares the costs and effects of one treatment (here, statin drug) with those of another (typically another statin drug). The ICER is defined as the difference in the cost of the each statin type divided by the difference in their effectiveness.

4. Results

The eligible study population consisted of 923 patients: 630 on Simvastatin, 155 Atorvastatin, 104 Rosuvastatin, 10 Fluvastatin and 24 Pravastatin. Several characteristics differed among the patients on statins (Table 3) showed that the mean

Table 3. Baseline characteristics of patients treated in clinical practice by therapy type

Characteristics	Simvastatin	Atorvastatin	Rosuvastatin	Fluvastatin	Pravastatin	Total	P-value
Number of subjects	630(68.26%)	155(16.79%)	104(11.27%)	10(1.08%)	24(2.6%)	923	
Sex							0.001
Male	274	85	60	3	17	439(47.56%)	
Female	356	70	44	7	7	484(52.44%)	
Age(year)							
Male	60.96	66.54	62.67	64	63.43		
Female	61.76	67.22	65.71	67.43	58.57		
Max	92	93	86	83	79		
Min	28	38	38	51	37		
Mean±SD	62.87±10.61	67.25±10.25	64.63±11.48	66.40±10.66	62.58±10.51	63.84±10.76	
Health benefit scheme							0.000
CSMBS		331(52.54%)	144(92.9%)	97(93.27%)	8(80%)	21(87.5%)	601
OOP		57(9.05%)	9(5.81%)	6(5.77%)	2(20%)	2(8.33%)	76
SSS		31(4.92%)	0	0	0	1(4.17%)	32
UC	211(33.49%)	2(1.29%)	1(0.96%)	0	0	214	
LDL-C parameter (mg/dL)							
LDL-C baseline, mean±SD	129.62±30.68	125.92±26.6	131.88±26.31	127.8±27.89	123.83±23.22	129.08±29.37	0.213
LDL-C final result, mean±SD	111.42±30.62	112.49±32.40	112.24±37.69	113.8±29.44	110.21±18.46	111.69±31.48	0.976
Annualized cost(Baht), mean±SD	1305.53 ±1244.81	16877.17 ±5796.87	19160.38 ±4559.23	12627.00 ±1848.60	15959.94 ±6174.01	6436.01 ±8205.43	0.000
Therapy duration(day), mean±SD	313.31 ±25.55	312.32 ±25.32	310.09 ±27.76	311.4 ±28.23	316.29 ±23.93	312.84 ±25.73	0.745

Table 4. Comparisons of number and percentage of patients achieving their LDL-C goal according to NCEP ATP III guidelines (LDL-C < 100 mg/dL) among statin therapy

Number of patients (%) achieving NCEP ATP III goal		
Statin therapy	Achieved	Total
Simvastatin	232(36.8)	630
Atorvastatin	60(38.7)	155
Rosuvastatin	41(39.4)	104
Fluvastatin	3(30)	10
Pravastatin	7(29.2)	24
Total	343(34.82)	923

P-value = 0.862

age was 63.84 years and 52.44% were female. Each health benefit scheme was differently used for statin type selection (P-value=0.000). Rosuvastatin and Atorvastatin were mostly prescribed for CSMBS patients. Simvastatin was prescribed for CSMBS and UC patients. Therapy duration showed that the mean was 312.84 days and this result was not significantly different between each statin (P-value = 0.745).

Mean LDL-C baseline was 129.08 mg/dL and Rosuvastatin had a higher baseline LDL-C level than other statins in this study but this result was not significantly different between each statin (P-value=0.213). Including mean LDL-C final was 111.69 mg/dL and Pravastatin had a lower final LDL-C level than other statin but this result was not significantly different between each statin (P-value = 0.976).

On the other hand, mean annualized cost was significantly different between each statin (P-value=0.000). Table 3 shows that Rosuvastatin was the most expensive statin, second order to Atorvastatin, Pravastatin, Fluvastatin and Simvastatin, respectively.

4.1 NCEP ATP III goal attainments

NCEP ATP III goal attainment is the LDL-C level less than 100 mg/dL for adults with diabetes which is considered

Table 5. Comparisons of cost-effectiveness in achievement of LDL-C goal according to NCEP ATP III guidelines among statin therapy

Statin therapy	Effectiveness % attain LDL-C goal	Annualized cost (Baht)	Annualized cost (USD)*	Mean annualized cost (USD)**	CER (mean annualized cost/ effectiveness)	ICER
Simvastatin	36.8	822,484.50	26,941.97	42.77	1.16	1.16
Fluvastatin	30	126,270.00	4,136.20	413.62	13.79	dominated
Pravastatin	29.2	383,038.50	12,547.12	522.80	17.90	dominated
Atorvastatin	38.7	2,615,961.00	85,690.55	552.84	14.29	3.16
Rosuvastatin	39.4	1,992,680.00	65,273.85	627.63	15.93	106.84

Remark:
*Annualized cost (USD), retrieved from electronic database at Phramongkutklao Hospital, based on the total annual cost (baht) of all patients/30.528
**Mean annualized cost based on annualized cost (USD)/number of patients.
Having eliminated Fluvastatin and Pravastatin, the ICERs were recalculated for Simvastatin, Atorvastatin and Rosuvastatin and are as shown in Table 6. Atorvastatin was dominated by Rosuvastatin as the latter was more effective and costs less to produce an additional unit of effect ($106.84 compared with $268.46) second after, Simvastatin. The dominated statin type, Atorvastatin, was then eliminated and the ICERs were recalculated (Table 7).

Table 6. Exclusion of more costly and less effective achievement of LDL-C goal

Statin therapy	Effectiveness % attain LDL-C goal	Mean annualized cost (USD)	Incremental cost (ΔC)	Incremental effect (ΔE)	ICER
Simvastatin	36.8	42.77	42.77	36.8	1.16
Atorvastatin	38.7	552.84	510.07	1.9	268.46
Rosuvastatin	39.4	627.63	74.79	0.7	106.84

Table 7. Exclusion of dominated statin type

Statin therapy	Effectiveness % attain LDL-C goal	Mean annualized cost (USD)	Incremental cost (ΔC)	Incremental effect (ΔE)	ICER
Simvastatin	36.8	42.77	42.77	36.8	1.16
Rosuvastatin	39.4	627.63	584.86	2.6	224.95

optimal. In this study was measured by comparisons of percentage of patients achieving LDL-C goal among statin therapy. The result in Table 4 showed that 34.82 % of patients using statin therapy can achieve LDL-C goals. Patients, who took Rosuvastatin, can achieve goal greater than patients was took other statins but, the differences were not statistically significant (39.4, 38.7, 36.8, 30 and 29.2%, respectively, P-value = 0.862).

4.2 Economic value assessment (cost-effectiveness)

In the base-case analysis, drug costs were based on retail statin prices at Phramongkultklao Hospital in 2011. The results in Table 5 show that Simvastatin had the lowest mean annualized cost ($42.77) and the most cost-effective, as indicated by the CER and the ICER, among outpatients with diabetes compared with other statins. Rosuvastatin had the highest mean annualized cost ($627.63) and Pravastatin was the highest CER. For the statin type interventions, the ICERs were calculated according to their cost from the least costly to the most, the ICER for Simvastatin worked out to be 1.16, Atorvastatin was 3.16, Rosuvastatin was 106.84, Fluvastatin and Pravastatin were dominated. Simvastatin was selected as the reference group because it had the lowest price compared with other group in this study.

5. Discussion

The result of this study indicates that Simvastatin is rather cost-effective compared with other statins and this

result is similar to assessments of the cost-effectiveness of statins in studies from the United States and United Kingdom (Heart Protection Study Collaborative Group, 2009 and Heart Protection Study Collaborative, 2006). This finding supports previous research, which links the article titled Statin cost-effectiveness in the United States for people at different vascular risk levels (2009) and the article titled Lifetime cost effectiveness of Simvastatin in a range of risk groups and age groups derived from a randomized trial of 20,536 people (2006) in the United Kingdom. The result suggested that 40 mg Simvastatin daily was rather cost-effective for people aged between 40 and 80 years with 5-year major vascular events risks (Heart Protection Study Collaborative Group, 2009) and the latter result proposed that Simvastatin was quite cost-effective for people aged between 35 and 85 years who have risk of vascular disease compared with no statin treatment (Heart Protection Study Collaborative Group, 2009 and Heart Protection Study Collaborative, 2006), respectively.

Likewise, the results of this study show that Simvastatin is a viable treatment alternative for achieving the LDL-C level goal for patients with diabetes because efficacy of reducing LDL-C is not inferior to other statins. This study has used the criterion of achieving the LDL-C goal to judge the treatment result (Table 4) instead of the amount of reduction in LDL-C although this is also interesting. This is because the focus of study is to see the LDL-C goal achievement using statin drugs. The choice of criterion is relevant to the goal, shows a clear difference and easy understanding. Future study may look into the absolute reduction of LDL-C with statin drugs. In addition this study included outpatients with diabetes both type 1 and 2 because the mean age of subjects was high (62.58-67.35) which is shown in Table 3 and the majority of Thai people with diabetes are type 2; thus, this study identifies LDL-C less than 100 mg/dL as optimal for achievement of the goal.

Even though Rosuvastatin has been shown in this present study to be the most efficacious monotherapy statin in lowering LDL-C level in the clinical practice and this result of efficacy is similar to many studies, also drug expenditure for statins needs to be considered and recognized in Thailand because statins were estimated as one of the top ten drugs left by quantity and expenditure in 2009 (Kaojarern *et al.*, 2011). Moreover, Thailand is low-middle income country where the government's budget is limited; thus, the five statins –Simvastatin, Atorvastatin, Rosuvastatin, Fluvastatin and Pravastatin – should be considered. These statins vary considerably in price so the statin type should be rationally selected. However, the chi-square test of this study showed that the difference in efficacy of these statins was not statistically significant. However, daily clinical practice may show the results that differ from clinical trials because medical personnel cannot strictly control their patient intake of food, compliance, lifestyle etc. In addition, this study did not draw data from random samples. Thus, the study could not specify patients with diabetes mellitus types. Generalizability of the results has to be concerned regarding this limitation. In the future work, this study should be further developed to randomized control trial.

6. Conclusion

In this investigation, the aim was to assess the cost-effectiveness of statin monotherapy in the clinical practice. The findings indicated that the use of Simvastatin is the most cost-effective therapy compared with Atorvastatin, Rosuvastatin, Fluvastatin and Pravastatin for outpatients with diabetes mellitus in attaining low-density lipoprotein cholesterol (LDL-C) goal. As a consequence, existing guidelines should be modified to increase for appropriate and cost-effective use of statin in the hospital as hospital-level guideline. Moreover, the pattern of this study should be applied for evaluation of other group drugs as a guideline for use in Thailand.

List of abbreviations and acronyms

ATP III	Adult Treatment Panel III
CEA	Cost-Effectiveness Analysis
CER	Cost-Effectiveness Ratio
CHD	Coronary Heart Disease
CSMBS	Civil Servant Medical Benefit Scheme
HDL	High Density Lipoprotein
HMG-coA	3-hydroxy-3-methylglutaryl coenzyme A
ICER	Incremental Cost-Effectiveness Ratio
LDL-C	Low Density Lipoprotein Cholesterol
Mg/dL	Milligrams per Deciliter
NCEP	National Cholesterol Education Program
OOP	Out Of Pocket
SSS	Social Security Scheme
TC	Total Cholesterol
TG	Triglycerides
UC	Universal health Coverage
USD	United States Dollars
WHO	World Health Organization

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