CHAPTER II

REVIEWS OF RELATED LITERATURE AND RESEARCH

1. Diabetes care

1.1. Basic knowledge about diabetes

Diabetes mellitus is a group of metabolic disease characterized by hyperglycemia resulting from insulin resistant, abnormal insulin secretion, or both. The main clinical symptoms of diabetes include weight loss, polyphagia (frequently hungry), polyuria (frequently urinating), polydipsia (frequently thirsty), blurred vision, severe fatigue, poor wound healing, dry or itchy skin, and recurrent infections [23]. The chronic high blood glucose level is associated with the damage in various organs and body systems including eyes, kidneys, nervous system, and cardiovascular system which result in many long-term complication including retinopathy, nephropathy, neuropathy, cardiovascular symptoms [23]. The clinical effects from diabetes which are defined as acute life-threatening are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome [23].

The most common type of diabetes is type 2 diabetes. The cause of type 2 diabetes is a combination of resistance to insulin action and an insulin secretion defect, while Type 1 diabetes, the less prevalent category, is an absolute deficiency of insulin secretion. There are the other types of diabetes which are rare including gestational diabetes mellitus(GDM), malnutrition-related diabetes and other types(e.g. drug induced, genetic defects) [23]

1.2. Importance of glycemic control

The American Diabetes Association (ADA) recommends that the patients with diabetes should control their A1c <7% [24].Asian-Pacific Type 2 Diabetes Policy Groups and International Diabetes Federation(IDF) also recommends that A1c target for glycemic control should not be more than 6.5% [9]. Both diabetes organization recommend like that because glycemic control is important not only for preventing acute

hyper- or hypoglycemia but also for helping the diabetes patient to reduce their long-term complication relating to diabetes progression. The result from the United Kingdom Prospective Diabetes Study (UKPDS) was shown that the median A1c values of 7%over 10 years controlled had significantly 25% risk reduction in aggregate microvascular endpoints(mainly different in cases of retinal photocoagulation) compared with another group(the median A1c ~7.9%) [8]. The diabetes control and complication trial (DCCT) have also shown that the treatment regimens that reduced average A1c to 7% was associated with fewer retinopathy, nephropathy, and neuropathy [25]. Furthermore, the result from a meta-analysis about A1c and cardiovascular diseases in 2004 [14] showed that an increase in A1c trend to increase cardiovascular disease. Therefore, it is important that all clinicians should try to control blood glucose of their diabetes patient for both short term and long-term outcome.

1.3. Assessment of glycemic control

The objective of diabetes therapy is to control the amount of blood glucose and maintain it like normal people. Blood glucose testing is the commonly used method but in some area that the blood testing is not available, so that urine testing is used. However, it can not detect hypoglycemia, and is not useful when the patients have some renal defect [9].

American Diabetes Association (ADA) recommends two techniques to assess the blood glycemic control including self-monitoring of blood glucose and glycosylated hemoglobin (A1c) test [24].

1.3.1. Self-monitoring of blood glucose

Self-monitoring of blood glucose is important because it can prevent asymptomatic hypo- and hyperglycemia. In addition, result of monitoring blood glucose can be useful in adjusting medical nutrition therapy and physical activity. The patients who use insulin usually need daily self glucose monitoring. However, as the accuracy of self-monitoring of blood glucose depends on user and instrument, health care providers have to carefully instruct the patients about technique in using the instrument. The health

care providers also need to teach the patients how to use the data from self-monitoring of blood glucose to adjust their dietary, physical activity and may be their medication therapy.

1.3.2. Glycosylated hemoglobin test

Glycosylated hemoglobin (A1c) is one of the standard parameter to determine the glycemic control in diabetes patient because it directly correlates with plasma glucose level. Rohfing et al [26] analyzed the result from the Diabetes Control and Complication Trial (DCCT) about the correlation between A1c level and mean plasma glucose. The results are shown in the table below.

Table1 Correlation between A1c level and mean plasma glucose levels on multiple testing over 2-3 months based on data from DCCT.

A1c (%)	Mean plasma glucose	
	mg/dl	mmol/l
4	65	3.5
5	100	5.5
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5

ADA has recommended that A1c should be tested approximately every 3 months to determine whether the patients can control their glycemic level within the target range [24]. However, the frequencies of testing depend on the clinical symptoms of the patients, and the determination of the clinicians.

1.4. Therapeutic options in diabetes

Therapeutic options in diabetes are both non-pharmacological treatment and pharmacological treatment targeted on glycemic control. Nonpharmacological treatment includes dietary control and exercise. Exercise improves insulin sensitivity or the ability to drive glucose into the cell [27]. It also decreases blood glucose by allowing glucose to penetrate to the muscle cell and be metabolized without the assistance of insulin, whereas dietary control is targeted on improved metabolic control. Pharmacologic treatments can be oral hypoglycemic agents, insulin, or both combinations. The oral hypoglycemic drugs can be categorized into 5 groups including metformin, sulfonylurea, α-glucosidase inhibitors, meglitinides (glinides), and thiazolidinediones (glitazones). Each of them has different mechanism and glycemic effect as summarized in table2. In addition to the oral hypoglycemic agent, insulin is usually added when the patients can not control their blood glucose. Moreover, insulin can use as a first-line therapy in patients whose diagnosis is not certain about their diabetes type.

However, commonly insulin should be combined with oral agent because the oral agent can limit weight gain, and reduce hypoglycemia associated with insulin therapy [24].

1.5. Guideline for diabetes management

Both ADA and IDF recommend that type 2 diabetes patients should start the therapy with non-pharmacological treatment (dietary control and exercise). If the glycemic target is not met, the patients should be added the oral hypoglycemic drugs. IDF recommends metformin for the overweight patients, while one or more of the five groups of the oral hypoglycemic drugs should be added in the non-obese. ADA recommends that only one of the hypoglycemic drugs should be added firstly but not recommends the specific drugs for the specific patient groups. If the patients can not control their blood glucose, the second one in the other groups should be added. Switching from an oral hypoglycemic drug to another is not recommended because it is not as effective as adding another group of hypoglycemic drugs. When the disease progress and glycemic target is not met again, insulin is recommended to be added.

After the final step of adding insulin, if the patients still have to take their oral hypoglycemic agent, insulin dosage should be adjusted until fasting plasma glucose (FPG) target is met. In addition, the oral hypoglycemic drugs may not work in everyone. Although most people can decrease their blood glucose level when they start to take an oral hypoglycemic drug, their blood glucose level may not be met the target. If the patient have had diabetes for more than 10 years or already taken more than 20 units per day of insulin, the oral hypoglycemic drugs may not help control blood glucose level [24].

Table 2 Oral hypoglycemic agents*

Oral hypoglycemic agent	Mechanism of action	Glycemic control effect	Common adverse effect
Biguanide (metformin)	• Reduce hepatic glucose production and glycogen metabolism in the liver. • Enhance insulin-mediated glucose uptake by skeletal muscle.	• Reduce HbA1c by 1-2% without Weight gain.	• Gastrointestinal disturbance • Lactic acidosis is a rare but serious side effect.
Sulfonylureas (chlorpropamide, glibenclamide,glimepiride, glipizide, glyburide, tolazamide, acetohexmide)	• Stimulate insulin secretion directly. • Decrease glucagons release. • Increase insulin receptor binding affinity. • Increase insulin effects by post-receptor action. • Decrease hepatic insulin extraction.	• Reduce HbA1c by 1-2%	• Hypoglycemia and weight gain
α-glucosidase inhibitors (acarbose, miglitol)	• Slow down carbohydrate absorption.	• Reduce HbA1c by 1% without Weight gain.	• Gastrointestinal disturbance
Meglitinides(glinides) (repaglinide, nateglinide)	• Stimulate insulin secretion from pancreas.	• Reduce post-prandial hyperglycemia.	• Hypoglycemia and weight gain
Thiazolidinediones (pioglitazone, rosiglitazone)	• Reduce insulin resistance in peripheral tissues acting as agonists of peroxisome proliferator-activated receptor-gamma (PPARgamma.) • Decrease hepatic glucose production.	• Reduce HbA1c by 1-2%	• Weight gain • Thiazolidinediones can have rare but serious effect on the liver.

* Data applied from ADA, IDF and other published sources.

ADA also recommends that there are no best drugs for every diabetes patient. The patients who start to have pharmacological therapy may need to try more than one type of the oral hypoglycemic drugs, combination oral hypoglycemic drugs, or combination the oral drugs with insulin. Both ADA and IDF have recommendations about the goal of controlling parameters for diabetes patients that are shown in table3.

Table 3 Recommendations for diabetes patients

Parameter	ADA recommendations	IDF recommendations
A1c	<7.0%	≤6.5%
Pre-prandial plasma glucose	90-130 mg/dl	80-110 mg/dl
	(5.0-7.2mmol/l)	(4.4-6.1mmol/l)
Peak post prandial plasma glucose*	<180mg/dl(<10.0mmol/l)	-
2-hour post prandial plasma glucose	-	80-145 mg/dl (4.4-8.0 mmol/l)
Blood pressure	<130/80 mmHg	<130/80 mmHg
LDL	<100 mg/dl(<2.6 mmol/l)	<97 mg/dl(<2.5 mmol/l)
Triglycerides	<150 mg/dl(<1.7 mmol/l)	<133 mg/dl(<1.5 mmol/l)
HDL	>40 mg/dl(>1.1 mmol/l)	>39 mg/dl(>1.0 mmol/l)

*Peak post prandial mean 1-2 h after the beginning of the meal.

2. Thiazolidinediones

2.1. Mechanism of action

Thiazolidinediones are oral antihyperglycemic agents that reduce insulin resistance in peripheral tissues and decrease hepatic glucose production [13] . In other words, there are insulin sensitizers that act as the agonists of the peroxisome proliferator-activated receptors-gamma (PPARgamma) (Figure1). Thiazolidinediones enhance the sensitivity to insulin in the liver, adipose tissue and muscle. This contrasts with sulfonylureas, which reduce blood glucose levels by stimulating the pancreas to secrete more insulin, and with metformin, which reduces blood glucose levels primarily by

lowering the rate at which glucose enters the circulation from the liver. Thiazolidinediones also have important non-glycemic effects such as modulation of lipid metabolism [13] . The drugs in this group for today market are rosiglitazone and pioglitazone.

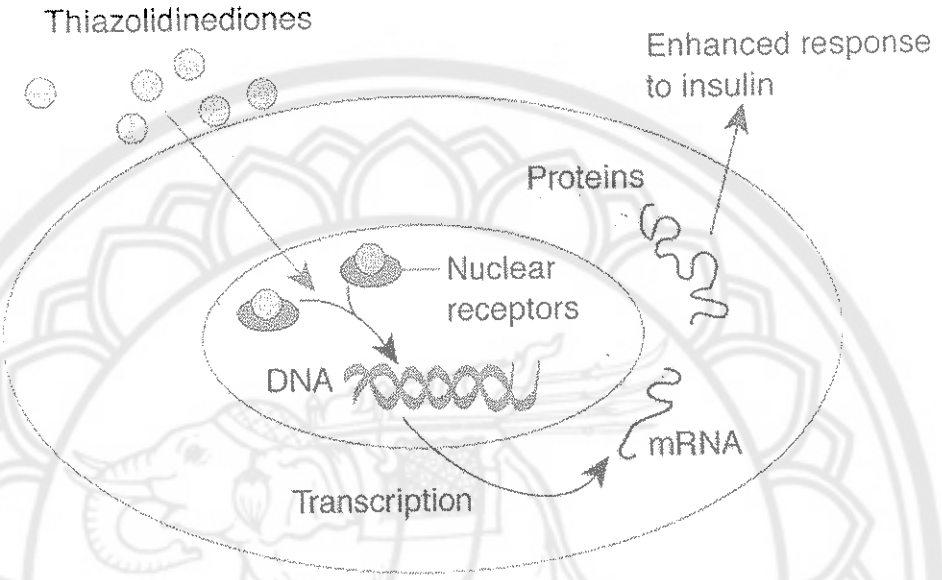

Figure1 Action of the thiazolidinediones on activation of the PPARγ receptor (This picture is copyright 2005 of Lippincott Williams & Wilkins. Retrieved from http://connection.lww.com /Products /porth7e/Ch43.asp)

2.2. Therapeutic effect of thiazolidinediones

Chiquette et al [14] conducted the meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors including A1c and lipid profiles. The result showed that both of thiazolidinediones had similar HbA1c decreases (1.0%-1.5%) and similar body weight increase approximately 3.0 kg. However, pioglitazone was more favorable in lipid profiles. Pioglitazone significantly decreased triglyceride level, increased HDL cholesterol (+4.6 mg/dL), and did not affected to LDL cholesterol and total cholesterol. Rosiglitazone significantly increased HDL cholesterol (+2.7 mg/dL), increased LDL cholesterol and total cholesterol, and neutral effect on triglyceride level (Table 4).

Table 4 Mean% change of A1c from baseline of thiazolidinediones in the Meta-analysis [14].

Drug	A1c(Mean% Change from baseline)	
	Monotherapy	Combination
rosiglitazone 4 mg	-0.90%(-1.42%to-0.38%)	-1.05%(-1.19%to-0.90%)
rosiglitazone 8 mg	-1.50%(-1.75%to-1.24%)	-1.26%(-1.48%to-1.04%)
pioglitazone 30 mg	-0.99%(-1.32%to-0.66%)	-1.16%(-1.41%to-0.90%)
pioglitazone45 mg	-1.21%(-1.79%to-0.62%)	-1.56%(-1.96%to-1.16%)

Table 5 Mean% change of A1c from baseline of the thiazolidinediones combination therapy in the Meta-analysis[14].

Treatment (Glitazones combinations)	Control (Comparators)	A1c(Mean% Change from baseline)		Treatment Length, wk
		Treatment	Control	
Pio+Ins	Ins+placebo	-1.3	-0.3	16
Pio+met	met+placebo	-0.7	(+0.2)	16
Pio+su	su+placebo	-1.2	(-0.1)-(+0.5)	16
Rosi+Ins	Ins+placebo	-0.6	(+0.1)	26
Rosi+met	met+placebo	(-0.6)-(-0.7)	(+0.3)-(+0.5)	26
Rosi+su	su+placebo	(-0.9)-(-1.4)	(-0.4)-(+0.2)	26

Pio=Pioglitzone 30 mg, Rosi=Rosiglitazone 4 mg, Ins=Insuline, su=Sulfonylureas, met=Metformin.

Table 6 Lipid effect of thiazolidinediones in the Meta-analysis[14]

Intervention	LDL	95%CI	TG	95%CI
Rosiglitazone	+15 mg/dl	13 to 18	-1mg/dL	-15to+12
Pioglitazone	-0.4 mg/dl	-5to4	-40mg/dL	-53to-26
Conclusion	R increased LDL P neutral effect		R neutral effect P decrease TG	
Intervention	HDL	95%CI	Total Chol	95%CI
Rosiglitazone	+2.71mg/dL	2.01to3.42	+21.3mg/dL	17.7to24.9
Pioglitazone	+4.55 mg/dl	3.61to5.48	-0.1mg/dL	-0.13to 0.13
Conclusion	R increased HDL P increased HDL		R increased total Chol P neutral effect	

R=Rosiglitazone, P=Pioglitazone, Chol= Cholesterol

2.3. Cost-effectiveness study of thiazolidinediones

There are many studies about cost effectiveness of thiazolidinediones [17], [18], [19], [20], [21], [22] . Most of study suggested that regimen using thiazolidinedione was cost-effective. The comparators of thiazolidinedione in the cost effectiveness studies included the treatment strategies using metformin, sulfonylurea, and acarbose (Appendix1-3). There was no study comparing between triple oral therapies. Dual combinations therapy was the most commonly used to compare. However, most of study stated that the evidence on long-term study of thiazolidinediones was rare. Therefore, the decision model projected the long-term outcome of thiazolidinediones was commonly used.

The incremental cost-effectiveness between both of thiazolidinediones was found in 2 studies [19], [22]. Both of studies suggested that pioglitazone was cost-effective. The using of pioglitazone was less expensive and more effective. In the study of Veenstra et al. [22] , the result of the model suggested that both monotherapy and combined therapy of pioglitazone dominated rosiglitazone. The other study in Henrikkson et al. [19] did not considers the monotherapy. The study evaluated cost-effectiveness in

patients who had failed with sulfonylurea or metformin monotherapy and thiazolidinedione was added. Henrikkson study compared pioglitazone 15 mg combinations with rosiglitazone 4 mg combinations and compared pioglitazone 30 mg combinations with rosiglitazone 8 mg combinations.

3. Economic evaluation in healthcare system

The limit of budget in an organization leads the policy maker to concern about the resource usage. Economic evaluation is the way to evaluate each spending budget in the optimized value. Cost (or budget) and consequences (or outcomes) are considered in economic evaluation [28]. In healthcare system, cost may be the cost of drugs or cost of interventions. Consequences may be efficacy of the drugs or heath quality of patients after receiving an intervention. Economic evaluation will be conducted if the interventions that we are interested have two or more choices. Costs are considered along with the consequences obtained from each spent cost. If the intervention has the lower value in consequences and the lower costs, it does not mean that we have to choose it.

3.1. Importance of perspective in economic evaluation

Before we conduct economic evaluation, we have to know who can take the benefit from our study .It is important because different perspectives are relevant to the different details in data collection. For example, the healthcare insurance company perspective may concern in which interventions, for the specific disease that they have to pay for their customer are cheaper. Therefore, costs that are related to this case are only cost that the insurance have to pay. It is costs for treating the specific diseases that do not include other cost that the patients have to pay themselves. When you have to conduct the cost-effectiveness study for a healthcare insurance, the cost that you have to collect is the direct medical cost including cost of the intervention, cost of laboratory tests, or other cost that the insurance covers. It is different from societal perspective that included all of relevant costs including cost of transportation to hospital, costs of lost of

productivity of the patient. In societal perspective, we have to collect all direct and indirect costs.

3.2. Types of economic evaluation

There are many types of economic evaluation. The difference are in the part of consequences or outcome [28]. If the outcomes of to interventions that we are interested are shown to be equivalent, the type of economic evaluation usage may be only cost analysis or cost-minimization analysis. Cost-benefit analysis is a type of economic evaluation thatconsiders the outcome in money value such as how much patients have the willingness to pay for the intervention. Cost-effectiveness analysis is the most commonly term used in economic evaluation. The outcomes used in cost-effectiveness analysis are the effect from the intervention on the patients including life year gains, length of stay in the hospitals, time to first event of a disease. The final type of economic evaluation is cost-utility analysis. The outcomes used in this evaluation type is different from cost-effectiveness analysis in which their weight the outcomes with utility score of the patient. The unit that is commonly used in cost-utility analysis is quality-adjusted life year gain (QALY). Some economic evaluation studies are preferred to use term of cost-effectiveness analysis representing cost-utility analysis.

3.3. Cost –estimation

Goal of cost estimation is to obtain the reasonable estimates of the costs for placing them in economic evaluation. There are two types of cost commonly used in economic evaluation. Firstly, direct cost is composed of direct medical cost and direct non-medical cost. Direct medical costs include cost of intervention, laboratory tests, health care labor, and medical facilities. They are most commonly used because they are the costs that are best understood by most health care decision makers. They have a direct financial impact on health care organizations. Direct non-medical costs are cost that we pay for non-health care resources. This cost is related to the loss in the time period that patients have to go to the hospital including cost of transportation to and from the hospital, child care cost for parents who have to hire someone for bringing up their

in productivity of the patients who have morbidity or mortality including tax losses resulting from reduced potential earnings of the patients. If we conduct an economic evaluation that outcomes or effectiveness are mortality or morbidity, we should not include the indirect cost of morbidity or mortality in the cost estimation to avoid a double counting.

Step in cost estimation will start with identifying resources. If we want to know cost of an intervention, we have to know what costs are related with the intervention. Cost of an intervention may include laboratory cost, cost of intervention itself, and cost of physician who provide intervention. We have to demonstrate all resources consumed and always keep the perspective in mind because cost will be different in different perspective. Next, we have to know the method that we will use to collect data. Cost data can come from various sources. There are many ways to collect cost data. Each cost collection method is different level of precision. Micro-costing is the most precision method. This method is conducted by collecting all components of the resource usage in a specific disease and calculating overall cost by the summation of each component cost. Case-mix group is the method that gives the cost for each category of disease. Precision of this method depends on the detail in a specific category. An example of case-mix group method is collection costs from Drug related groups (DRGs). Disease-specific per day is the method that gives the average daily cost for broad category disease group such as daily cost in orthopaedic surgery. The final method is average per day. This method give average cost for all categories of patients such as average cost for out-patient visit. When we have to choose the cost estimation methods, we have to consider which precision we need and which cost is available. In practically, a disease may have many related costs. The mixed cost methods are commonly used. After we collect all relevant data available, valuation resources is the final step. We have to know what the value of data that we have. For example, if the data are charge, we must change it to cost by using cost to charge ratio method. For the effect of different time of collection data in each source, we have to adjusted cost value to the same time by using consumer price index.

3.4. Effectiveness (outcome)

Effectiveness or outcome in the economic evaluation can be expressed in many different terms including life years gain, QALYs, case of disease prevented. Because cost-effectiveness analysis and cost-utility analysis are the most commonly term used in economic evaluation, the effectiveness in this part will not state the monetary value. The effectiveness in cost-effectiveness analysis have to provide in a real practice value because the result of analysis is aim to apply it in the real world, not a specific setting situation. Therefore, the effectiveness is commonly calculated from different sources combining clinical trials, observational studies, or even experts opinion. It depends on which source is available. The effectiveness is always the final outcome of the patients including the effect of disease on morbidity or mortality. The final outcome used in the economic evaluation is different from commonly outcome in clinical trials. The outcomes of clinical trials are always intermediate or surrogate outcome.

In practical treatment, there are commonly found that the surrogate outcomes can not predict the final outcomes as in the clinical trial hypothesis [29]. The possible pathways of relationship between surrogate outcome and true clinical outcome (final outcome) are shown in Figure 2.

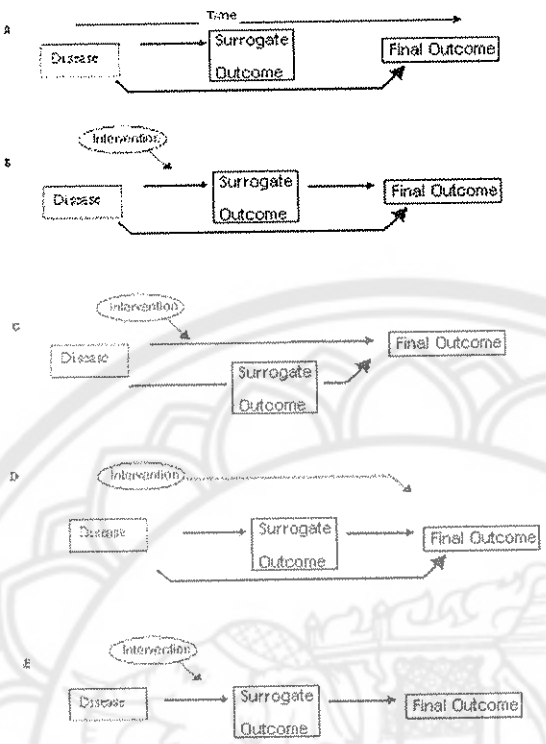

Figure 2 The possible pathways of relationship between surrogate outcome and final outcome.

A. The surrogate end-point is not related with the real disease progressive pathway. B. There are several disease progressive pathways. The intervention affects only one pathway that mediates through the surrogate end-point. C. The intervention affects another pathway that does not mediate through the surrogate outcome. D. The intervention affects another pathway that does not relate with both the surrogate pathways and the other disease progressive pathways. E. The intervention affects the pathway that is the only one pathway of the disease. Although Fig 2E represents the pathway that surrogate outcome is the most accepted for considering the effectiveness of the intervention, the surrogate outcome can make some error conclusions. For example, if we measure a surrogate outcome that is considered effective to predict the final outcome of the chronic diseases in only short-time period, we may not conclude the result. Some interventions can affect the surrogate outcomes in short duration but can not affect the surrogate outcome in the long duration. Therefore, if we have final outcomes data, it is worthwhile to use it for the effectiveness of cost-effectiveness

analysis. However, there are the limited sources of final outcome because it always takes long time period to collect the data. Data from the clinical trials that report the surrogate outcomes may be used for estimate the final outcomes. In addition, although we have the final outcomes directly from clinical trials such as survival, the data may require some adjustments. For example, if the clinical study reports the final outcome as survival at one year, extrapolation to more than one year have to use some methods to calculate and may need some other data for adding. Thus, modeling techniques are always used in cost-effectiveness analysis.

4. Disease modeling

International society for pharmacoeconomic and outcomes research (ISPOR) gave the definition for disease modeling or healthcare evaluation modeling that it is an analytic methodology that accounts for events over time and across populations[30]. The data can come from both primary and secondary sources. Purpose of modeling is to estimate the effects of intervention on valued health consequences and costs that are of interest to health-care decision makers. Sources for modeling are from clinical trials, observational studies, insurance claim databases, case registries, public health statistics, and preference surveys. The value of modeling has become more widely accepted as one of evidence for submissions for new interventions in many countries around the world including Australia, Belgium, Canada, Germany, Italy, the UK and The USA [31] .

4.1. Types of model

There are many different ways to describe type of model. In this part we will consider in analytical aspects. Firstly, decision tree model is the simplest model. It is the instrument that is used to calculate the different outcome between two or more choices. Probabilities and expected value of having outcomes in each choice are used to incorporate into the model. The expected outcomes are shown at the end of each branch of the tree representing the expected outcome of each intervention choice. For example, in Figure 3, there are three treatment choices for patients. The end of each branch is the

expected value of the final outcome. Dead value is equal to zero. Live is equal to one. We have to collect the probabilities of each treatment branch to calculate the expected value of each branch. There are many heath economic studies using decision tree model. However, decision tree model is not suitable for recurrent events or chronic diseases. It is commonly used to evaluate the outcomes for acute of short-term diseases.

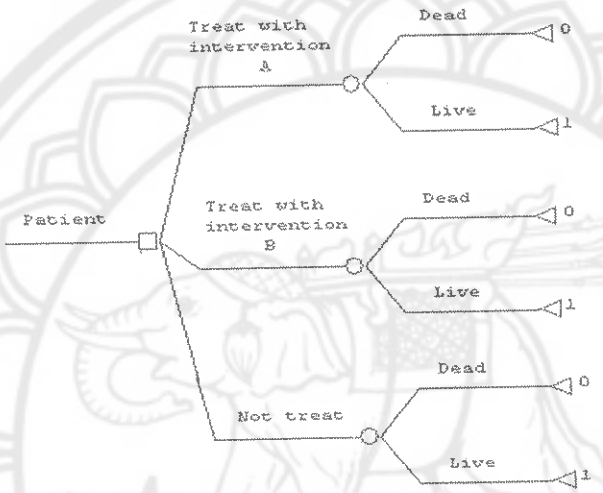

Figure 3 Decision tree model

State-transition model or Markov model is another model (Figure 4). It can be used in long-term and recurrent diseases. A chronic disease commonly has many health states. In Markov modeling, we have to know the probabilities which patients will change to each states or stay in the same states over a period of time. The probabilities are called transition probabilities. Another thing that I have to know is the outcome in each state. After we have both transition probabilities and outcomes for each state, we can calculate outcomes over the time period. Transition probabilities and outcomes data are commonly derived from the literatures.

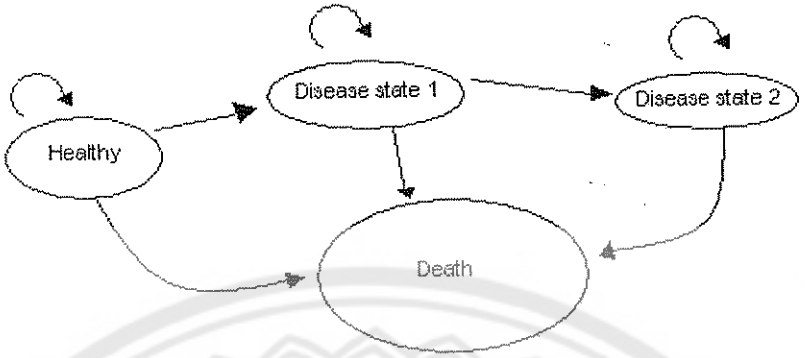

Figure 4 Markov model

4.2. Sensitivity analysis

Every health care evaluation model has uncertainty because there are always many assumptions for the final outcome of the new interventions. As we stated about the surrogate outcome in part 3.4, there may be many factors that have an impact on the surrogate outcomes and also the final outcomes. We can consider whether the factors have an impact on the outcomes or not by incorporating each factor in sensitivity analysis.

Sensitivity analysis is the method for allowing uncertainty. Drummon et al [28] has recommended three steps in sensitivity analysis. Firstly, we have to identify the factors that we need to analyze. Secondly, we have to find the possible range of each factor that affects our outcome in the evaluation. Finally, we will calculate the analysis on the combinations of the most possible value, the upper bound, and the lower bound of each factor. There are two types of sensitivity analysis that are commonly seen in the economic evaluation studies. One-way sensitivity analysis estimates that only one factor is uncertain and calculates the different results of our study by varying the factor. Multi-way sensitivity analysis estimates that more than one factor are uncertain. In multi-way sensitivity analysis, there are many uncertain factors, so that the combinations of variety factors are very large and difficult to interpret. In practical, multi-way sensitivity analysis may be only two-way.

4.3. Diabetes models

As we stated above that diabetes relates with many complications, diabetes modeling commonly has many topics to concern about their complexity. Three things that we may concern before using the model are their clinical data used in the models, transparency of the models, and their analytical abilities. Firstly, the clinical data that incorporate into the model might be related with all possible complications of diabetes. The relationships between the surrogate outcomes from clinical trials and the final outcomes may be understudied. Secondly, the models should be transparent. Transparency of the models means that the models have to show all structures of the models. The models that are considered transparent may show all data enough to reproduce. However, in fact, most diabetes models are always too complex too understand all of the relevant calculating data. Finally, analytical abilities of the models should be understood before we start to use them. The models should have flexibility for answer varied type of diabetes questions and should have the ways to manage uncertainly of study results. American Diabetes Association (ADA) Consensus Panel published Guidelines for computer modeling of diabetes and its complications in 2004 [32]. The guidelines indicated how to make users to gain confidence that a modeling study, and the model itself, accurately represent the "real" world. Description of the model's structure, inputs, equations, and algorithms, assumptions, and data sources should be provided so that others can understand how the model is built and applied. There are many different types of models that are applicable to diabetes [31], [33], [34], [35], [36], [37], [38] and have been used to address a variety of clinical and economic questions [32] . The comparison of some models has been described in detail elsewhere [32].

4.4. The CORE diabetes model

The CORE Diabetes Model is the diabetes model that has been conducted by the Center for Outcomes Research (CORE) in Switzerland. In the model[31], studies were selected based on the criteria that they provided the appropriate data, most recent and largest studies available (UKPDS, DCCT, Framingham, ISDR, etc.). The probabilities

in the model can be altered without any re-programming to suit user preference or incorporate newly published data. The model projects outcomes for populations, taking into account baseline cohort characteristics and past history of complications, current and future diabetes management and concomitant medications, screening strategies, and changes in physiological parameters over time. The development of complications, life expectancy, quality-adjusted life expectancy and total costs within populations can be calculated.

One of the differences between The CORE Diabetes Model and other models is sub-modeling. In the CORE Diabetes Model, there are 15 sub-models. Each sub-model is Markov model using time-, state-, time-in–state and diabetes type-dependent probabilities to simulate the progress of patients through different states. The sub-models simulate the following complications: angina, cataract, congestive heart failure, foot ulcers and amputation, hypoglycemia, ketoacidosis, lactic acidosis, macular edema, myocardial infarction, nephropathy, neuropathy, peripheral vascular disease, retinopathy, stroke and non-specific mortality. There is one additional sub-model, which is not related to complications. It is the type 2 diabetes treatment sequence sub-model. This model simulates changes in the treatment pathway over time due to treatment failure and/or side effects of treatments to control hyperglycemia in simulations of type 2 diabetes. In addition, the use of Monte Carlo simulation with tracker variables allows the interaction between sub-models in order to simulate accurately the relationship between the development and progression of multiple complications within individual patients.

Although the ISPOR recommended that the structure of the model should be as simple as possible[30], the CORE diabetes sub-modeling looks large and complex compared with the previous models. However, each sub-model is reasonable and understandable. Examples are eyes complications. For the previous models eyes complication sub-model is only retinopathy, but the CORE diabetes has three sub-models related with eyes complications, including retinopathy, macular edema, and cataract. The sub-models are different to each other, including state in each sub-model, risk adjustments, and transition probabilities. Based on ADA's special requirements of

diabetes modeling [32], some diabetes complications, such as blindness, impose small costs on payers but large indirect costs on patients and their families. Therefore, authors and users of models should select their perspective carefully and explicitly state it in their analysis.

Another important topic that both ISPOR and ADA guidelines recommended is validation. If the models are transparent and validated, it assures that predictions made by the model are correct. The CORE Diabetes Model compare results from published epidemiological and clinical studies in type 1 and type 2 diabetes [39]. For the first validation, the model was designed, programmed and validated by an experienced team specialized in diabetes disease modeling, in cooperation with diabetologists from the University Hospital Zurich. A total of 66 second-(internal) and third-(external) order validation analyses are also performed. Studies are chosen that, collectively, spanned a range of patient populations, treatments, delivery settings and outcomes, as well as a variety of diabetic complications and time periods (from 1960 to 2003).

The CORE Diabetes Model was validated with varied published studies, including studies from Asia population (the Osaka study of type 2 diabetes in Japan).It assured that the model is better used for Thai people than some of previous model that do not include Asia population. In addition, the model is readily accessible over the internet, which allows users to perform accurate simulations as and when required.