CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Design

This study was an analytic study using a state-transition model "Markov model". Data from clinical and epidemiological studies were exploited. In case of no data available, expert opinions were obtained.

3.2 Population

To simulate Markov models, the patient data from the study by Ravid and colleagues were employed. The inclusion criterion for this study were patients with the following characteristics:

1. NIDDM, diagnosed according to World Health Organization criteria;
2. age less than 50 years;
3. duration of diabetes mellitus less than 10 years with no evidence of systemic, renal, cardiac, or hepatic diseases;
4. body mass index less than 27 kg/m^2;
5. normal blood pressure values on two consecutive examinations (systolic, $\leq$ 140 mm Hg; diastolic, $\leq$ 90 mm Hg;);
6. serum creatinine $<$ 123 μmol/L (1.4mg/dL)
7. microalbuminuria (urinary protein excretion of 30 to 300 mg/24 hour on two consecutive visits without evidence of urinary tract infection).

3.3 Methods

This study compared two alternatives for delaying progression of diabetic nephropathy (DN) in NIDDM patients with the early stage of progression of DN (microalbuminuria). These alternatives were:

Alternative 1(drug): Treating patients with an ACE-Inhibitor (using enalapril 10 mg once daily), taken by those in the stage of microalbuminuria only.

Alternative 2 (conventional therapy or no drug): Controlling blood glucose, without taking any ACE-Inhibitors.

Markov models of progression of DN in NIDDM patients with microalbuminuria consist of mutually exclusive states. The stages of nephropathy were shown in figures 3.1 and 3.2.

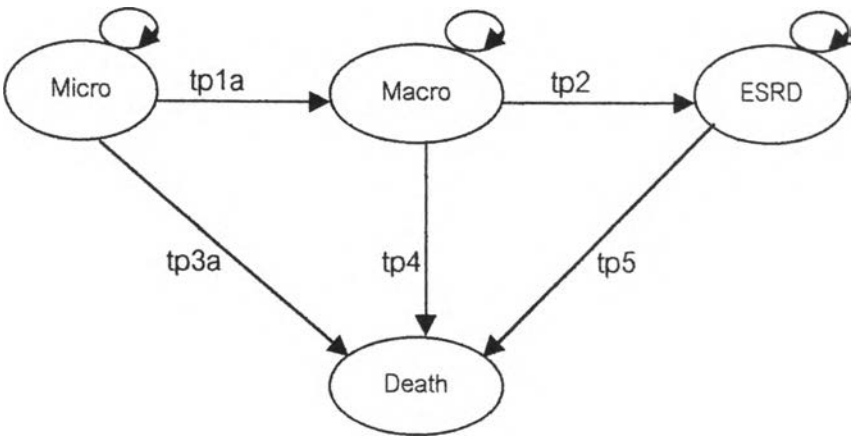

Figure 3.1 Model of Nephropathy in NIDDM for Alternative 1 (Drug)

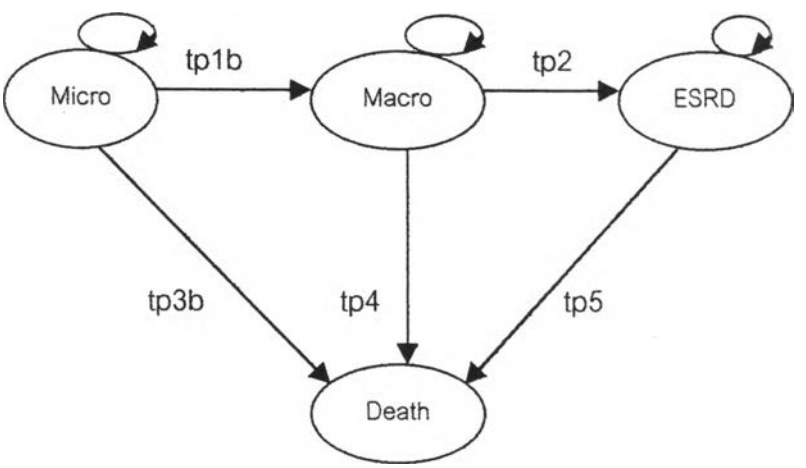

Figure 3.2 Model of Nephropathy in NIDDM for Alternative 2 (No Drug)

The models illustrated the stages of diabetic nephropathy, assuming that the patient (here, assumed to be 44 years of age according to Ravid's study) began at the stage of microalbuminuria, which was the early stage of progression of DN. Oval symbols in the figures represented states of health; arrow signs represented the possible transitions between health states. The patients progressed from microalbuminuria to macroalbuminuria and ESRD. Those with ESRD ultimately died of renal failure or cardiovascular disease (CVD). The patients in all other states might die of CVD or other causes unrelated to diabetes. An arrow pointing backward on top of each state indicated that a patient could remain in that particular state. The expected course of nephropathy was simulated in a Markov model and the description of transition to each other state was shown in table 3.1.

Table 3.1 Description of Transition

Transition Probabilities	Transition	
	From	To
tp1a	Microalbuminuria	Macroalbuminuria
tp1b	Microalbuminuria	Macroalbuminuria
tp2	Macroalbuminuria	ESRD
tp3a	Microalbuminuria	Death
tp3b	Microalbuminuria	Death
tp4	Macroalbuminuria	Death
tp5	ESRD	Death

Note: a = for drug therapy, b = for no drug therapy

Transition probabilities, which dictated the movement of the patients through disease states, were derived from available data and estimated by expert opinion

3.3.1 Transition Probabilities from Microalbuminuria to Macroalbuminuria (tp1a and tp1b)

Tp1a and tp1b were taken from a randomized controlled study conducted across 7-year period by Ravid et al (1996). This study was conducted in Israel and it was one of two long-term trials available and accepted by physicians. This study was chosen because the characteristics of the subjects were more similar to Thai people than another study conducted in India (Ahmad et al, 1997). The data from the study showed that the cumulative incidence from microalbuminuria to macroalbuminuria for enalapril-treated group and untreated group was equal to 18% and 60%, respectively. In other words, treatment with enalapril resulted in risk reduction of 42% of nephropathy development during 7 years.

3.3.2 Transition Probability from Macroalbuminuria to ESRD (tp2)

Tp2 was derived from a longitudinal study conducted by the National Institute of Diabetes and Digestive and Kidney Disease, Phoenix, Arizona, USA. This study was done in Pima Indians with NIDDM and macroalbuminuria to determine factors related to the development of ESRD after the onset of macroalbuminuria and its incidence. It was found that the cumulative incidence of ESRD was 40 % in 10 years after the onset of macroalbuminuria. Experts believe that there are similarities of the characteristics of NIDDM between Pima Indians and Thai patients. This leads to the decision that this data could be applied to Thai NIDDM patients.

With this data, transition probabilities over a Markov cycle were calculated. In this study the length of a cycle was set equal to one year. Since the probabilities available did not refer to the same period of time as the Markov cycle chosen, the following formula could be used

$$tp1 = 1-(1-tpt)^{1/t}$$

Where tp1 was the yearly transition probability and tpt was the overall probability over time period t.

For example, to calculate transition probability from microalbuminuria to macroalbuminuria for drug group over one year, with the cumulative incidence of 18% in 7 years, tp1a was

$$= 1-(1-0.18)^{1/7}$$

$$= 0.02795/yr$$

The same method was applied to calculate tp1b and tp2.

3.3.3 Mortality Rates of Microalbuminuria and Macroalbuminuria (tp3a, tp3b, and tp4)

Since there was no data available on mortality rate of NIDDM patients in the stage of microalbuminuria and macroalbuminuria, the method of asking clinician experts was used. Five nephrologists from the Nephrology Society of Thailand were selected. Three questions were developed to ask for mortality rate of NIDDM patients relative to general population. The questions were validated by the physicians. These questions were:

1. How many folds increase or decrease in mortality rate in NIDDM patients with microalbuminuria with or without ACE-Inhibitor treatment compared to general population?

2. How many folds increase or decrease in mortality rate in NIDDM patients with macroalbuminuria compared to general population?

With the information on patient characteristics provided, the experts were to answer these questions. The answers were shown in table 3.2.

Table 3.2 The Number of Times of Mortality Rate from Expert Opinion

Expert	Microalbuminuria			Macroalbuminuria
	Drug	No drug	Difference	
1	1	1	0	5
2	1.3	2	0.7	10
3	1	1	0	2
4	1	2	1	5
5	1.5	2	0.5	4
Mode	1	2	0	5
Mean	1.16±0.21	1.6±0.53	0.44±0.39	5.2±2.64
Median	1	2	0.5	5

From these data, median was used to estimate mortality rate. Thus, the selected figures for microalbuminuria (drug), microalbuminuria (no drug) and macroalbuminuria were 1,1.5 (1+0.5), and 5 respectively. For mortality rate of general population, age specific mortality rate of Thai people in 1996, the latest data of mortality rate available from public health statistics Ministry of Public Health, was utilized.

The formula for calculating age specific mortality rate is:

$$= \frac{\text{The number of deceased population aged X}}{\text{The number of population aged X in mid year}} * 1000$$

Hence, mortality rate of Thai people aged 45-69 was calculated as following:

$$= \frac{\text{The number of deceased population aged 45-69}}{\text{The number of population aged 45-69 in mid year}} *1000$$

$$= \frac{111{,}664 \ *1000}{11{,}020{,}475}$$

$$= 10.13/1000$$

$$= 1.013\% \text{ or } 0.01013$$

To calculate the transition probability over one year, for example from microalbuminuria to death for no drug therapy, 1.5, the figure obtained from expert opinion, was multiplied by 0.01013. In order to calculate tp3a and tp4, the same method was employed.

3.3.4 Mortality Rate of ESRD (tp5)

This data was obtained from the study conducted at Pramongkutklao hospital (Wutthichumnong et al, 1998). The mortality rate of ESRD in diabetes patients who underwent hemodialysis was 60 % in 2 years. The transition probability from ESRD to death over one year was calculated using the formula in the section 3.3.3. Mortality rates of ESRD as well as other transition probabilities in this study were assumed to remain constant over time.

3.3.5 Cost Data

Costs were considered from the point of view of patients who were responsible for their direct medical costs. Only the cost of treatment of ESRD was included. Costs of other diseases affected by the intervention were assumed to be equal for both alternatives. Hence, there were two main costs as following:

a) The cost of drug therapy

Enalapril was selected as a prototype of ACE-Inhibitors in this study. The drug price of the original product (Renitec®) was exploited throughout the whole study. In addition, because in Thailand enalapril was in the national essential drug list, it had a

medium price. This meant if the drug company of original enalapril would like to sell its drug to public hospitals, it had to sell the drug at the medium price even the price list was much higher.

Therefore, to estimate the cost of drug therapy, there were two prices of enalapril representing the cost of drug therapy as following:

1. Medium price of enalapril 5 mg (1998) = 159.50 baht per 30 tablets
   or = 5.32 baht per tablet 5mg
2. Wholesale price of Renitec® 5 mg (1998) = 217.80 baht per 30 tablets
   (From Merck Sharp and Dohme)
   or = 7.26 baht per tablet 5mg

Normally, public hospitals in Thailand put approximately 20% mark-up on the purchased price. In this study the costs associated with treatment of side effects as well as the costs of drug monitoring, for example lab test, were excluded.

Hence, an annual cost of drug therapy (enalapril 10 mg/day) was equal to 4,660 baht (5.32*2*365*1.2) for medium price and 6,360 baht (7.26*2*365*1.2) for wholesale drug price, respectively.

b) The cost of renal morbidity (the cost of treatment of ESRD)

In this study, the cost of hemodialysis was employed to represent the cost of treatment of ESRD because the majority of ERSD patients in Thailand underwent this procedure. The data on hemodialysis cost were obtained from a Master's thesis, Mahidol University, Bangkok, Thailand (Homwijitkul, 1998). The average cost of hemodialysis was 35,000 baht per month (direct medical cost). As a result, an annual hemodialysis cost was assumed to be 420,000 baht (35,000*12).

To simulate Markov models, the models were programmed on DATA TreeAGE software. A Markov model would be evaluated by matrix algebra as a cohort simulation, as shown in tables 3.3 and 3.4. Since Thai people 's life expectancy was 69 years at the time of this study, the length of the studied cycle, for which costs and health outcomes was measured, was 25 cycles or 25 years. After 25 cycles all of patients in the cohort were assumed to die because the mortality rate of Thai people after the age of 69 was significantly increased.

For discounting, in modern economics, people pay interest expenses when they borrow money and receive interest payments when they lend or save. Thus, money paid in the future is worth less than money today, and for health interventions whose costs are spread over many years or whose savings are spread over many years, the practice of discounting is essential.

On the health benefit side, economists who work on cost-effectiveness analysis have long accepted the health effects should be discounted in the same way that the expenditures are and that the same discount or interest rate should be used (Gold et al, 1996). Therefore, in this study, it was assumed that the interest rate was 8% per year so all costs and health outcomes were discounted at 8% per annum.

The reason for discounting health effects, for example future life years saved, is not that life years can be invested to yield more life years as money can be invested to yield more money. It is not necessary to assume that life years in the future are less valuable than life years today. Rather, the reason for discounting future life years is that they are being valued relative to the money and, since the money in the future is discounted relative to the present money, so must a life year in the future be discounted relative to the present money (Weistein and Stason, 1977).

Table 3.3 Transition Matrix for the Markov Model of Drug Therapy

Transition	To				Total
From	Micro	Macro	ESRD	Death	
Micro	0.96192	0.02795	0	0.01013	1
Macro	0	0.89955	0.0498	0.05065	1
ESRD	0	0	0.63246	0.36754	1
Death	0	0	0	1	1

Table 3.4 Transition Matrix for the Markov Model of No Drug Therapy

Transition	To				Total
From	Micro	Macro	ESRD	Death	
Micro	0.86211	0.12269	0	0.01520	1
Macro	0	0.89955	0.0498	0.05065	1
ESRD	0	0	0.63246	0.36754	1
Death	0	0	0	1	1

Note: This representation is useful only if the transition probabilities remain constant over time

Table 3.5 Conclusion of Parameter Values for Markov Modeling

Variable	Value	Reference	Source of data	Method of data collection
Transition Probabilities				
tp1a	0.02795/yr	Ravid et al 1996	Secondary data	Literature review
tp1b	0.12269/yr	Ravid et al 1996	Secondary data	Literature review
tp2	0.0498/yr	Nelson et al 1993	Secondary data	Literature review
tp3a	0.01013/yr	Expert opinion	Primary data	Interview
tp3b	0.01520/yr	Expert opinion	Primary data	Interview
tp4	0.05065/yr	Expert opinion	Primary data	Interview
tp5	0.36754/yr	Wutthichumnong et al 1998	Secondary data	Literature review
Costs				
C Drug	4,660 baht/yr	Medium price	Primary data	Interview
	6,360 baht/yr	wholesale price 1998		
C ESRD	420,000 baht/yr	Homwijitkul 1998	Secondary data	Literature review

Note: yr = year

3.4 Data Analysis

This analysis compared the progression of diabetic nephropathy and medical care costs incurred with drug treatment summarized as life expectancy and lifetime medical costs with the same outcomes under no drug treatment. Cost-effectiveness was the ratio of the incremental costs (the net increase in health-care costs) to the incremental effectiveness (the net improvement in health outcome). The lower the value of this ratio was, the higher the priority of the program in terms of maximizing benefits derived from a given health expenditure would be. If the value of incremental cost-effectiveness ratio (ICER) was positive, the intervention under study incurred additional costs and produced enhanced health outcomes relative to the existing alternative. On the other hand, if the intervention resulted in less cost and more health outcomes than the alternative, the value of ICER would be negative, meaning cost savings.

ICER was calculated from the following formula:

$$ICER = \frac{C_T - C_C}{E_T - E_C} = \frac{\Delta C}{\Delta E}$$

Where C_T and E_T were the costs and effectiveness of drug treatment and C_C and E_C were the costs and effectiveness of no drug treatment. These quantities would be estimated from the Markov models.

The index of cost-effectiveness could be summarized as:

$$\frac{\Delta C}{\Delta E} = \frac{\Delta C_{(RX+MORB)}}{\Delta Y}$$

Incremental costs (ΔC) included additional direct medical costs related to the new program. There were cost of drug treatment (ΔC_{RX}) and ΔC_{MORB} representing savings in medical costs due to the reduction in morbidity accomplished by the new program. In this study, the reduction in events of ESRD was considered.

Incremental effectiveness (ΔE) was the health effectiveness of the new program as the net change in years of life expectancy (ΔY).

Life expectancy was reported without discounting but cost-effectiveness ratios incorporated discounting of costs and life expectancy.

Furthermore, sensitivity analysis was undertaken to examine the cost of the drug, the cost of treatment of ESRD, the discount rate, and the effect of the drug