CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 What is diabetes?

Diabetes mellitus is a chronic disease caused either by deficiency in production of insulin by the pancreas or by ineffectiveness of the insulin produced. Such a deficiency results in increased concentration of glucose in the blood (hyperglycemia) which in turn leads to damage to many of the body's systems, especially the blood vessels and nerves.

There are basically two main forms of diabetes; the insulin-dependent (IDDM), also known as Type 1 diabetes, and non-insulin-dependent (NIDDM), also known as Type 2 diabetes. In IDDM, the pancreas fails to produce the insulin, which is essential for survival. This form develops most frequently in children and adolescents. NIDDM is much more common and accounts for about 90% of all diabetes cases worldwide. In Thailand, NIDDM accounts for about 95% of all diabetes (Wannee Nitiyanant et al, 1991). This form occurs principally in adults and results from the body's inability to respond properly to the action of insulin produced by the pancreas. Lifestyle changes and Westernization accompanying economic development in developing countries have been followed by substantial increases in the prevalence of NIDDM.

1.1.2 Symptoms of Diabetes

The symptoms of diabetes may be pronounced or subdued. In IDDM, when fully developed, the classic symptoms are excessive secretion of urine, thirst, weight loss and a feeling of lassitude. These symptoms may be less marked in NIDDM. In this form it

can also happen that no early symptoms appear and the disease is only diagnosed several years after its onset when complications are already present.

1.1.3 Treatment of Diabetes

People with IDDM are totally dependent on insulin injections and require daily administration of insulin. The majority of diabetic patients have NIDDM. However, up to 30% of them may use insulin injections occasionally or regularly to control their conditions. Controlling food intake, exercise, and insulin or oral hypoglycemic medication regulates diabetes. People with diabetes are usually advised to keep their blood glucose concentrations as near to normal as possible.

1.1.4 Diabetic Complications

In the short term, very high levels of blood glucose can cause diabetic ketoacidosis, a metabolic disturbance with potentially fatal consequences, which mainly affects people with IDDM. Another severe short-term diabetic condition is hypoglycemia. This happens when blood glucose levels become too low as a result of the administration of too much insulin, too much exercise or insufficient food or carbohydrate intake. Hypoglycemia is frequent in insulin-treated subjects, but can also happen to people using oral hypoglycemic drug therapy.

In the longer term, excess blood sugar causes irreparable damage to the blood vessels, the heart, kidneys, eyes and nervous system, and represents a major threat to the health and life of those with diabetes. It is these complications which make diabetes such a serious, long-term and costly condition.

1.1.5 Costs of Complications

Much of the direct cost of diabetes is attributable to the need to treat the complications of the disease. From several studies, more than 70% of the hospital cost of people with diabetes can be attributed to chronic complications. Table 1.1 shows an overview of the distribution of costs for the hospital treatment of diabetic complications in the USA in 1987.

Table 1.1 Hospitalization Costs of Diabetic Complications in the USA, 1987

	Attributable episodes	Mean costs per day (US$)	Mean LOS* (days)	Total costs (US$ million) Absolute	relation %
Neuropathy	35,859	596	8.6	184	3.6
Diseases of the veins	5,798	510	7.7	23	0.5
Diseases of the arteries	68,567	884	14.4	873	17.1
Cerebrovascular accident	71,863	639	10.8	496	9.7
Heart disease	355,521	891	7.5	2,376	46.7
Renal Disease	72,743	703	10.0	511	10.0
Ophthalmic disorders	20,574	1066	3.4	75	1.5
Other and unspecified	155,978	507	7.0	554	10.9
Total	786,903			5,092	100.0

* LOS : length of stay

From table 1.1, heart disease is the major chronic complication of people with diabetes, followed by renal disease which has increased sharply in recent years. If we take 70,000 people with diabetes who are likely now to be suffering from end stage renal disease (ESRD) in the USA and annual treatment costs of US$ 45,000 per capita, the total direct cost for ESRD would be more than US$3 billion. (A report of the Diabetes Health Economics Study Group)

1.2 Rationale

In 1985, WHO estimated that 30 million people around the world had diabetes. WHO now estimates that diabetes affects approximately 130 million people worldwide with an estimated 90% of these individuals being likely to have NIDDM. Due to population aging and further urbanization, a rise to approximately 300 million is predicted by the year 2025, most of this increase occurring in the developing countries.

The increase in the prevalence of diabetes and its complications, in addition to decreasing the quality of life of individuals and their families, will have severe economic consequences for them and for society. Thus, all countries should be encouraged to develop national policies and programs for the prevention and control of this costly disease.

Diabetic Nephropathy, due to a progressive microvascular complication from diabetes, is a major threat to people with diabetes. The final stage of the slow deterioration of the kidneys is referred to as ESRD. The cost of treatment of ESRD is very high, namely the cost of dialysis, which causes a burden to patients and society as well.

Diabetic Nephropathy is the most common cause of ESRD, accounting for about one-third of new ESRD cases in the United States. For Thailand, In 1995, Nephrology Society reported that twenty-two percent of patients undergoing dialysis were the result of diabetes. In addition, the incidence of new cases of ESRD is rising in all countries.

Regarding natural history, there are five stages in the progression of diabetic nephropathy as shown in table 1.2

Table 1.2 Natural History of Diabetic Nephropathy

Stage	Characteristic	Onset (years)
1	Initial diagnosis(Hyperfiltration)	0
2	Silent stage (Normoalbuminuria)	2-3
3	Microalbuminuria (Incipient Nephropathy)	6-7
4	Macroalbuminuria (Overt Nephropathy)	15-18
5	End stage renal disease	25

Source: Mogensen et al, 1983

The concept of microalbuminuria has had a major impact on diabetes research. Microalbuminuria is an established predictor of progression of nephropathy and early mortality in both IDDM and NIDDM (Mogensen, 1984). Angiotensin Converting Enzyme (ACE) Inhibitors, an antihypertensive drug group, have been found to attenuate progression of nephropathy in both types of diabetes in hypertension and normotension with microalbuminuria (Viberti and Chaturvedi, 1997).

As noted before, diabetic nephropathy is the leading cause of ESRD. If we can prevent or slow progression of diabetic nephropathy, it will reduce the number of patients with ESRD. As a result, it should reduce the burden to the patients and the society as a whole. Prevention of diabetic renal disease, or at least the postponement or slowing down of the disease process has emerged as a key issue. Using ACE-Inhibitors at early stage of diabetic nephropathy (microalbuminuria) is a powerful strategy to prevent progression of renal disease in NIDDM patients with microalbuminuria, even when blood pressure is normal (Mogensen et al, 1995) However, most previous economic evaluation studies have been performed in IDDM. Hence, an economic evaluation of ACE-Inhibitors in NIDDM patients for this indication should also be done to provide information to physicians, patients and policy makers to assist in decisions making.

1.3 Research Questions

If treatment with an ACE-Inhibitor at the early stage of diabetic nephropathy (microalbuminuria) in NIDDM can delay the development of end stage renal disease, what the effect on patient survival and what the cost of this intervention will be.

1.4 Research Objectives

1.4.1 General Objective

To evaluate cost-effectiveness of an ACE-Inhibitor for delaying progression of diabetic nephropathy in non-insulin-dependent diabetes mellitus patients with microalbuminuria under well blood glucose control.

1.4.2 Specific Objectives

1) To determine medical costs over lifetime of conventional (no ACE-Inhibitors) and ACE-Inhibitor therapy
2) To determine effectiveness of conventional (no ACE-Inhibitors) and ACE-Inhibitor therapy in terms of life expectancy
3) To evaluate cost-effectiveness ratio in terms of incremental cost per life year saved

1.5 Scope of the Study

This study will be limited to non-insulin-dependent diabetes mellitus patients (NIDDM) with microalbuminuria. Subjects will have to well control their glucose levels and have normal blood pressure.

Moreover, only the effect of ACE-Inhibitors on preventing renal disease will be studied, not including cardiovascular disease. Studies on the effects of ACE-Inhibitors on cardiovascular disease in NIDDM are not currently available. Costs in this study are in perspective of patients.

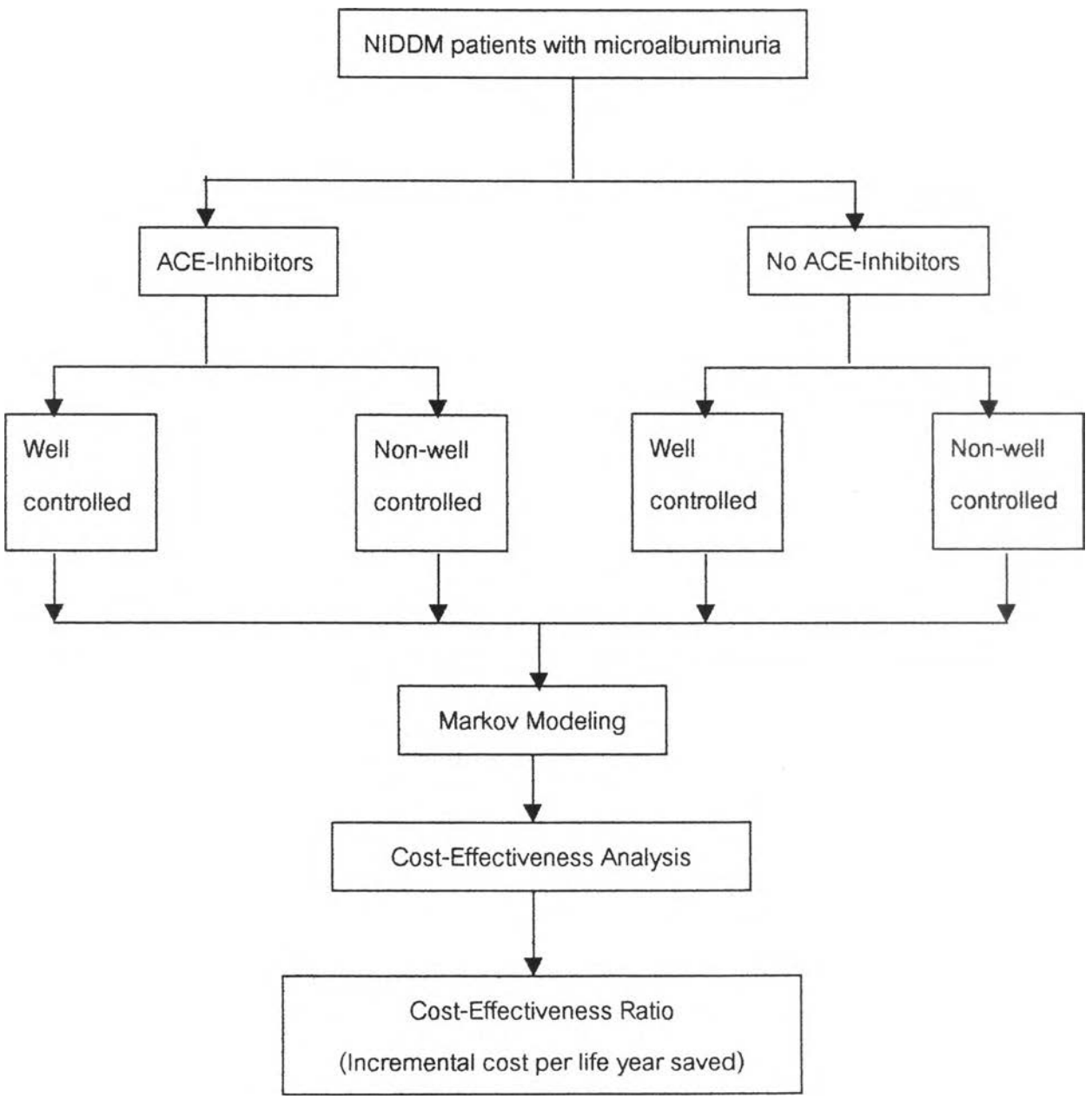
1.6 Conceptual Framework

In this study, firstly, NIDDM patients are in the stage of microalbuminuria prior to receiving ACE-Inhibitors or no ACE-Inhibitors. The patients are divided into four groups according to figure 1.1. Each alternative has two types of patients, well or non-well controlled.

Only well-controlled patients are studied because data available from clinical trials of ACE-Inhibitors was for well blood glucose control (Ravid et al, 1996) as shown in figure 1.2. However, the effect of the drug under well blood glucose control will overestimate the effectiveness of the drug in the whole population. Therefore, sensitivity analysis will be performed to speculate the real cost-effectiveness in the population where their compliance of blood glucose control might not always be perfect.

In addition, Markov modeling will be employed to determine medical costs in perspective of patients over lifetime and effectiveness in terms of life expectancy in both ACE-Inhibitor and no ACE-Inhibitor therapy. Finally, cost-effectiveness ratio of an ACE-Inhibitor will be expressed in terms of incremental cost per life year saved.

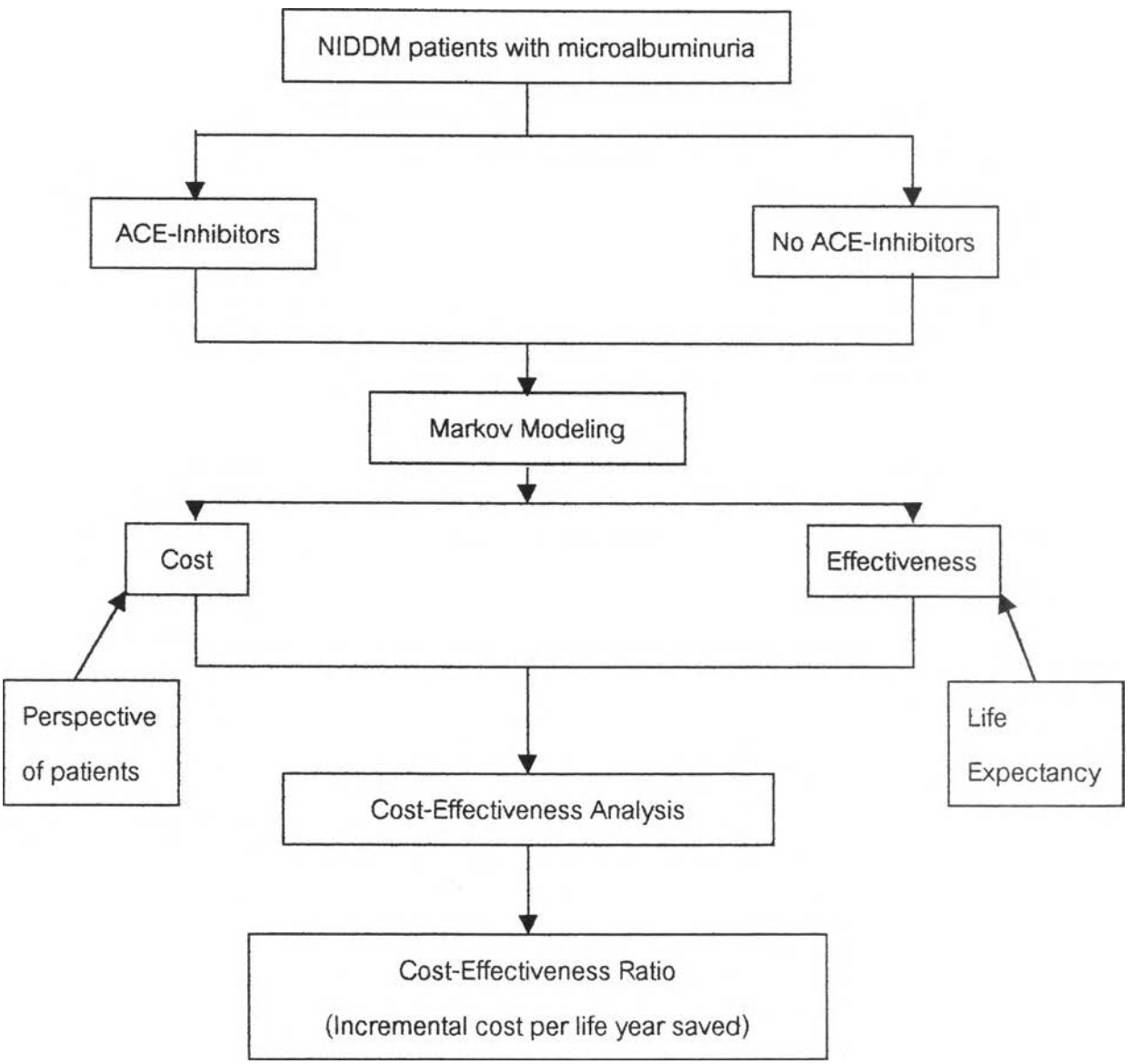
Figure 1.1 Conceptual Framework for Cost-Effectiveness Analysis of an ACE-Inhibitor for Delaying Progression of Diabetic Nephropathy in NIDDM Patients with Microalbuminuria



Note: Well controlled means Well blood glucose control

Non-well controlled means Non-well blood glucose control

Figure 1.2 Conceptual Framework for Well-Controlled Groups



1.6.1 Markov Modeling for Economic Evaluation

In this study, decision analytic modeling is used to estimate costs and effectiveness. The model which should be utilized is a state-transition model, for example Markov models. Health economists are beginning to use Markov models widely in economic evaluation studies.

Markov models are useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once. Representing such clinical settings with conventional decision trees is difficult and may require unrealistic simplifying assumptions (Sonnenberg and Beck, 1993).

Markov models are often employed to represent stochastic process that is random processes that evolve over time. In healthcare context, Markov models are particularly suited to modeling chronic disease (Briggs and Sculpher 1998).

In chronic disease like diabetes, events such as complications of the chronic disease or its treatment are confronted repeatedly during a lifetime. Decision tree models are not well suited to represent recurrent events that repeat over time (Gold et al, 1996). Thus, from the reasons above, Markov models are used to perform economic evaluation in this study.

1.6.2 Constructing a Markov Model of Disease Progression (Briggs & Sculpher, 1998)

Markov models assume that a patient is always in one of a finite number of discrete health states called Markov states. All events are represented as transitions from one state to another. Hence steps for constructing a Markov model are as follows:

1 Define the disease in terms of different states

For example, suppose that the model consists of just 3 states to characterize a chronic disease.

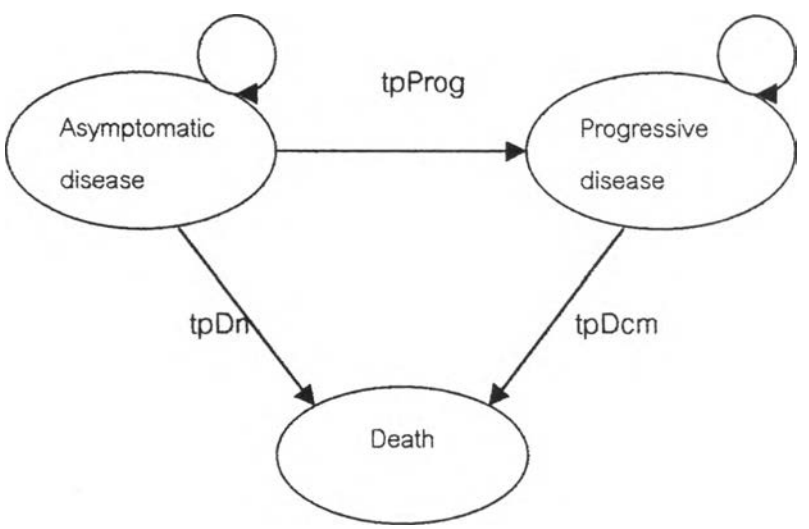


Figure 1.3 Illustrative Markov Model of Disease Progression

Disease states are represented by ovals and arrows show possible transitions between those states. The backward bending arrows show that it is possible for patients to remain in the states they were in during the previous cycle.

The states should be mutually exclusive since one of the requirements of a Markov model is that a patient cannot be in more than one state at any one time. In addition, these states should be chosen to represent clinically and economically important events in the disease process that is to be modeled.

2 Transition Probabilities assigned for movement between states over a discrete time period known as "a Markov cycle"

In a model comprising k states, all possible transitions between those states are given by k x k transition matrix. For example, in the model illustrated, there are 3 states and 9 possible transitions between those states. However, it is assumed that patients do not recover from their progressive disease, so transitions from dead to progressive disease, progressive to asymptomatic disease are ruled out.

Also, since the probability of moving to states in each cycle must sum to 1, the probability of staying in the same state in a given cycle is 1 minus the probability of leaving that state. Therefore, of the 9 possible transitions in our model, we have only to estimate 3 transition probabilities:

1. Moving from the asymptomatic to the progressive disease state (tpProg)
2. Dying when in the asymptomatic state from a condition other than the disease (tpDn)
3. Dying when in the progressive disease state (tpDcm)

Table 1.3 Transition Matrix for the Illustrative Model

Transition from	To Asymptomatic	Progressive	Death	Total
Asymptomatic	1-tpProg-tpDn	tpProg	tpDn	1
Progressive	0	1-tpDcm	tpDcm	1
Death	0	0	1	1

There are two different types of Markov models characterized by the form of the transition probabilities as follows:

1. Markov Chain – All transition probabilities are assumed to be constant over time. These can be calculated by raising the transition matrix.
2. Markov Process – All transition probabilities can vary over time known as time-dependent transition probabilities. These are less convenient to represent in terms of matrix algebra.

Moreover, a limitation of the Markov model is that the probability of moving out of a state is not dependent on the states a patient may have experienced before entering that state. This is the "memoryless" feature of Markov models often referred to as the "Markovian assumption". It is important to be aware of this assumption since it may be seen to be limiting in some cases.

Another problem is that probabilities available in the literature may not refer to the same period of time as the chosen Markov cycle. Supposedly, a published probability of death over 5 years as the basis for a death transition probability is used to estimate in a Markov model based on a yearly cycle. The yearly transition probability cannot be simply estimated by dividing the 5-year probability by 5 since this will overestimate the 5-year probability of a transition due to the effect of compounding. The following formula is used:

$$t_{p1} = 1-(1-t_{pt})^{1/t}$$

Where t_{p1} is the yearly transition probability needed to estimate and t_{pt} is the overall probability over time period t.

3 Attaching estimates of resource use and health outcome to the model

In order to complete the Markov model, it is necessary to attach weights to the model for the cost and health outcome quantities to be estimated. For example, to predict life expectancy, a weight of 1 is attached to each state of the model in which the

patient is alive and a weight of 0 is attached to the dead state. Running the model over a large number of cycles and summing the weights across those cycles gives an estimate of the average life expectancy of the patient in terms of the model cycle length. This can be multiplied by the length of the cycle in years to give life expectancy in years.

To calculate costs over the lifetime, the costs of spending 1 cycle in each of the states of the model are attached to that state and the model is run over a large number of cycles and the total cost obtained by summing across those states.

4. Discounting

It is standard practice in economic evaluation to adjust costs and outcomes for differential timing by applying a rate of discount which allows comparisons of costs and outcomes in terms of a net present value (NPV). The standard discounting formula is given by:

$$V_0 = \frac{V_t}{(1+r)^t}$$

Where V_0 is the equivalent current value at time zero (or NPV), V_t is the value at time t and r is the rate of discount.

Since Markov models deal explicitly with the dimension of time, they allow discounting of costs and outcomes at the point in time that they occur in the model. Hence, providing the appropriately constructed model, Markov models will automatically discount both costs and outcomes correctly, with the cycle number (in years) feeding in directly to the formula above.

1.6.3 Cost and Effectiveness Data

Ideally, data on the costs and effects of an intervention should both be collected from the same designed primary study. However, this ideal is frequently not a feasible design for a cost-effectiveness analysis given the goals of the analysis and the financial constraints for most studies. In general, primary designs are most feasible for the interventions with short-term effects, for example a new therapy to treat migraine headaches.

When a primary cost-effectiveness study is not feasible, effectiveness and cost data can be gathered from separate sources. These sources may be primary or secondary and they may employ a variety of study designs. For effectiveness data, prospective sources are often preferred, although not always. Data on resource use are infrequently gathered in formal trials, so other secondary sources such as administrative or claims databases are more commonly used.

When data are gathered from separate sources, the analyst will generally rely on mathematical or simulation models to combine the information into a structure based on the conceptual model. As a rule, interventions with long-term consequences including most prevention programs require synthesis of data from diverse studies and a modeled projection of outcomes into the future like this study.

1.6.4 Future Costs in Cost-Effectiveness Analysis (Gold et al, 1996)

To clarify the issues, three categories of induced costs that may or may not be involved in a CEA are defined as follows:

1. Costs related to the intervention, which are incurred during years of life that would have been lived without the intervention. These costs, related disease

in the original life span, are not controversial. They must be included in the analysis, for example cost of treating complications.

2. Costs unrelated to the intervention, which are incurred during years of life that would have been lived without the intervention. These costs, unrelated health and nonhealth costs occurring during the original life span, are also not controversial. They are the same with and without the intervention. It is usually preferable to exclude them.

3. Costs that occur in years of life added (or subtracted) by the intervention. The third categories may be subdivided further into three subcategories as follow:
   a) Health care costs for the disease or diseases affected by the intervention. These are costs for diseases related to the intervention but occurring in added years of life. These are typically included in CEA. For example, the costs of an ongoing treatment during added years of life, such as lifelong antihypertensive therapy are always included.
   b) Health care cost for other diseases. These are costs for diseases unrelated to the intervention and occurring in added years of life. This has been the source of much controversy. These costs may be excluded or included.
   c) Nonhealth costs in added years of life such as food, shelter, and clothing. These may be excluded or included.

1.7 Definitions

1. State-transition models: Models which allocate, and subsequently reallocate members of a population among several categories or health states. Transitions from one state to another occur at defined, recurring time intervals according to transition probabilities. Through simulation or mathematical calculation the number of members of the population passing through each

state at each point in time can be estimated. State-transition models can be used to calculate life expectancy or quality-adjusted life expectancy.

2. Markov models: A type of mathematical model containing a finite number of mutually exclusive health states, having time periods of uniform length, and in which the probability of movement from one state to another depends on the current state and remains constant over time.
3. Health state: The health of an individual at any particular point in time. A health state may be modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment, or health policy.
4. Cost-effectiveness analysis: An analytic tool in which costs and effects of a program and at least one alternative are calculated and presented in a ratio of incremental cost to incremental effect. Effects are health outcomes, such as a disease prevented, years of life gained, or quality-adjusted life years gained, rather than monetary measures as in cost-benefit analysis.
5. Incremental cost-effectiveness ratio: The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.
6. Effectiveness: The extent to which medical interventions achieve health improvements in real practice settings.
7. Costs: The value of health care resources consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it. Costs in this study are in perspective of patients referring to the expenditure.
8. Health-related quality of life: As a construct, health-related quality of life (HRQOL) refers to the impact of the health aspects of an individual's life on that person's quality of life or well–being. Also used to refer to the value of a health state to an individual.

9. Quality-adjusted life years (QALYs): A measure of health outcome, which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period. A weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.

1.8 Possible Benefits

This study can be used as a tool in decision making for both prescribers and policy makers in a reimbursement program. This study can also provide information for patients regarding the value of the drug. The result of the study can also lead to development of clinical practice guidelines for managing diabetes as well as considering ACE-Inhibitors in hospital drug formularies for this condition.

1.9 Limitations of the Study

Because this study is a modeling design it has clear limitations, which may reduce the value of this study. Modeling designs draw on existing literatures as a source of secondary data on costs and intervention effects relevant to the subject of the study. Often, cost and effect data or event probability data have to be obtained from more than one source. When few studies have been done, estimates based on expert opinion are used as inputs to the model. Estimates incorporated into the analysis may be inaccurate, whether derived from data or based on expert opinion.

For example, in this study, only one reliable clinical study available is utilized to represent the effect of an ACE-Inhibitor in delaying progression of diabetic nephropathy in NIDDM. In addition, mortality rates in each stage of diabetic nephropathy are derived from interviewing experts. As noted earlier, these data may be inaccurate.

Another limitation in this study is the constraint of employing Markov models in which probability remains constant over time. This may not be true in the real practice. Using time-dependent values can solve this problem but there have been no data about time-dependent probability. Moreover, using time-dependent probability will create a sophisticated process and it is not possible to do within time limitation. Therefore, in this study all transition probabilities are assumed to be constant over time.