CHAPTER 2

LITERATURE REVIEW

Several clinical studies of the effects of ACE-Inhibitors to slow progression of diabetic nephropathy in NIDDM patients were undertaken. Previous studies on economic evaluation of ACE-Inhibitors in diabetic nephropathy, most of which were done in IDDM patients, in terms of objectives, methodology, and results, were also reviewed These are as follows:

2.1 The Clinical Effects of ACE-Inhibitors in NIDDM with Microalbuminuria

The first sign of diabetic nephropathy is a persistent increase in the albumin excretion rate to 20 to 200 μg/min (30 to 300 mg/day). The phenomenon is called microalbuminuria. Microalbuminuria is a marker of early vascular damage in micro and macrovascular, so it is a powerful predictor of renal and cardiovascular disease in both IDDM and NIDDM. In adult diabetic patients, microalbuminuria indicates early diabetic nephropathy. Studies of secondary prevention have shown that blood pressure lowering drugs reduce albumin excretion rate. Angiotensin converting enzyme inhibitors are particularly effective in reducing the risk of progression to macroalbuminuria in both IDDM and NIDDM. Whether this postpones the onset of end stage renal disease and/or reduces early mortality in these patients remains to be established (Viberti and Chaturvedi, 1997).

In contrast to the situation with IDDM, relatively few studies have investigated the effects of ACE-Inhibitors in NIDDM patients with microalbuminuria even though the majority of diabetic patients are NIDDM patients. There are few studies of the effects of ACE-Inhibitors conducted in NIDDM patients. Enalapril is the most extensively used ACE-Inhibitor. One study demonstrated that low-dose enalapril (5mg/day) reduced the

urinary albumin rate (UAE) without affecting systemic blood pressure in normotensive and well-controlled hypertensive NIDDM patients (Sano T et al, 1994). A randomized, double blind placebo-controlled trial of ramipril (1.25 mg/day) in 122 normotensive or mildly hypertensive NIDDM patients with microalbuminuria provided evidence of the effectiveness of low-dose ACE inhibition in arresting the progressive rise in albuminuria in this condition after 6 months' treatment (Trevisan et al, 1995).

In the first long-term trial of ACE-Inhibitors in this setting, Ravid et al, in 1993, conducted a 5-year, randomized double-blind comparison of enalapril with placebo in 94 normotensive NIDDM patients (aged 36 to 49 years) with microalbuminuria. Enalapril produced an initial reduction in microalbuminuria, followed by stabilization over 5 years, whereas placebo treatment was associated with a steady rise in UAE rate from 123 to 310 mg/day. Importantly, the decline in renal function, expressed as the reciprocal of the serum creatinine concentration, was halted by enalapril, and only 12% of patients developed diabetic nephropathy. In contrast, 42% of placebo developed diabetic nephropathy. Continuation of this study, adopting an open follow-up protocol for a further 2 years, revealed that the renoprotective benefits of enalapril persisted with continuous therapy over this additional period, whereas discontinuation of enalapril resulted in renewed progression of nephropathy. Over the 7-year treatment period, enalapril significantly reduced the absolute risk of developing nephropathy by 42% (Ravid et al, 1996). Ahmad et al (1997) showed that enalapril initiated during the period of microalbuminuria could decrease the number of patients progressing from microalbuminuria to macroalbuminuria reduced by 66.7% after five years.

2.2 Economic Evaluation of ACE-Inhibitors in Diabetic Nephropathy

In 1992, Siegel et al studied cost-effectiveness of screening and early treatment of nephropathy in patients with insulin-dependent diabetes mellitus because the preliminary analysis suggested that the early treatment of IDDM patients with ACE-Inhibitors is likely to be a very cost-effective use of health care resources. They used a

diagnosed IDDM patients. They found that cost-effectiveness ratio for screening and treatment at stage of microalbuminuria ($7,900 to $16,500 per year of life saved) compared favorably with those of other medical life-saving interventions. Less aggressive programs (screening followed by treatment at the stage of microalbuminuria) would improve life expectancy to a lesser extent but could save net health care costs as well as years of life.

In 1995, Kiberd and Jindal examined the conditions necessary to make screening for microalbuminuria in IDDM patients cost effective. This economic evaluation compared two strategies designed to prevent the development of end stage renal disease in IDDM patients with disease for five years. Strategy A, screening for microalbuminuria as currently recommended, was compared with strategy B, a protocol in which patients were screened for hypertension and macroalbuminuria. Patients identified in both strategies were treated with ACE-Inhibitors. The method was computer simulation (Markov model) and outcome measures were strategy costs and quality adjusted life years (QALYs). The model predicted that strategy A would produce an additional 0.00967 QALYs at a present value cost of $261.53 (1990 US$) per patient or an incremental cost/QALYs of $27,041.69 over strategy B.

In 1996, Rodby et al used the results from a randomized, placebo-controlled trial comparing 207 captopril (a drug of ACE- Inhibitors) patients with 202 placebo patients, whose purpose was to determine whether captopril has kidney-protecting properties independent of its effect on blood pressure in diabetic nephropathy to develop a model of medical treatment for patients before progression to ESRD. To model the course of illness after progression to ESRD and to extend the model to patients with NIDDM, they used data from the U.S. Renal Data System and published literature. Medical resource cost data were based on Medical reimbursement levels, published wholesale drug prices, and surveying health care providers. The economic model used a payer

perspective to estimate direct cost. The cost to society (indirect cost) associated with lost patient productivity due to ESRD was also estimated.

They found that treatment with captopril resulted in an absolute direct cost saving or benefit of $32,550 per patient with IDDM over the course of a lifetime compared to treatment with placebo. For patients with NIDDM, the direct cost savings totaled $9,900 per patient. Absolute savings were found for indirect costs as well: $84,390 per patient with IDDM and $45,730 per patient with NIDDM. They concluded that the use of captopril in diabetic nephropathy would provide significant savings in health care costs; in addition, it would result in savings in indirect cost, which reflected the broader social benefit.

In 1996, The Diabetes Control and Complication Trial Research Group (DCCT) examined the cost-effectiveness of alternative approaches to the management of IDDM. A Monte Carlo simulation model was developed to estimate the life benefits and costs of conventional and intensive insulin therapy. Data were collected as part of the DCCT and supplemented with data from other clinical trials and epidemiological studies. Approximately 120,000 persons with IDDM in the United States meet DCCT eligibility criteria. Implementing intensive rather than conventional therapy in this population would result in a gain of 920,000 years, 691,000 years free from end-stage renal disease, 678,000 years free from lower extremity amputation, and 611,000 years of life at an additional cost of $4 billion over the lifetime of the population. The incremental cost per year of life gained was $28,661.

In 1997, Hendry et al developed an economic model to analyze the cost impact of ACE-Inhibitors treatment on progression to ESRD in diabetic patients over 4 years. Two scenarios were compared: one describing the progression of a cohort of 1,000 patients receiving 25 mg captopril three times daily, and the other for an equivalent cohort without such prophylactic treatment. Previously published data were used to

estimate the transition rates for each stage from the onset of renal failure until death. All direct costs were discounted by an annual rate of 6%, and were subjected to sensitivity analysis. The discounted cost saving of ACE-Inhibitor treatment for a cohort of 1,000 patients was estimated that as 0.95 million pound over 4 years. Prophylactic treatment with ACE-Inhibitors was predicted to provide substantial increases in life expectancy and reduction in the incidence of ESRD, while also providing significant economic savings.

In 1998, Kiberd and Jindal studied how effective ACE-Inhibitors must be in preventing diabetic nephropathy to warrant routine administration to insulin-dependent diabetic patients. A Markov model was used to compare three strategies designed to prevent the development of ESRD in insulin-dependent diabetic patients. Strategy 1, screening for microalbuminuria and treatment of incipient nephropathy as currently recommended, was compared with strategy 2, a protocol in which patients were routinely administered an ACE inhibitor 5 years after diagnosis of diabetes, and strategy 3, in which patients at high risk for nephropathy were routinely treated and low risk patients followed a protocol in which patients were treated with an ACE Inhibitor if they developed hypertension and/or macroalbuminuria.

The model predicted that strategy 2 would produce as many quality-adjusted life years as strategy 1 at nearly the same cost if routine drug therapy reduced the rate of development of microalbuminuria by 26% in all patients. Strategy 3 produced as many quality-adjusted life years at less cost than strategy 1 if a high-risk cohort could be identified with a rate of developing microalbuminuria at four times the rate of low risk patients and if drug therapy reduced the rate of developing microalbuminuria in this high risk group by 20 %. In conclusion, routine ACE Inhibitor therapy could prove to be cost-effective, especially if high-risk individuals could be identified.