PATIENT PREFERENCES FOR ANTIHYPERTENSIVE THERAPY IN A COST BENEFIT ANALYSIS CONTEXT: THE ROLE OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN TREATMENT CONSIDERATIONS FOR HYPERTENSION

by

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(Under the Direction of Randall Tackett)

ABSTRACT

The objectives of this study were to 1) determine the relative importance of the attributes of the Angiotensin Converting Enzyme Inhibitors (ACEIs) and to 2) measure the indirect willingness to pay (WTP) for improvements in ACEI attributes. A cross-sectional, telephone survey adapted discrete choice experiment was conducted using the Georgia Poll. The average respondent in this survey was white, female, with an average household income of between $35,000 and $49,999 per annum. The relative importance of ACEI attributes was risk of side effects, dosage schedule, efficacy and cost respectively. Respondents are WTP $179.32/ month for reduction in risk of side effects, WTP $52.02/ month for improvement in efficacy and respondents are WTP $61.78/ month for improvement in dosage convenience. In conclusion, this study establishes the relative importance of ACEI attributes and shows that patients are willing to participate in antihypertensive treatment choice.

INDEX WORDS: Patient preferences, Discrete choice experiment, Willingness to pay, Georgia poll, Telephone survey, Treatment choice

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CHAPTER ONE

INTRODUCTION

1.1 Introduction

The economic, social and health system impact of cardiovascular disease in the United States (US) is enormous (Thom et al., 2006; Elliott, 2003). Health care spending in the US has risen steadily over the past few decades due in part to the high prevalence of cardiovascular diseases such as hypertension (Thorpe, 2005). Also, the total cost of cardiovascular disease in 2006 was estimated to be 18% of the 2006 US National Health Expenditure of $2.9 trillion (Thom et al., 2006; Borger et al., 2006). Physician office visits, nursing home stays and hospital visits for cardiovascular disease in 2006 were projected to cost $195.7 billion in 2006 (Thom et al., 2006). Over the last 2 decades, cardiovascular diseases have ranked highest among all disease categories in hospital discharges (Thom et al., 2006). Therefore, cardiovascular diseases place a substantial strain on personal, societal and health system resources (Zyczynski & Coyne, 2000; Cushman, 2003).

Hypertension presents significant challenges to the US health care system (Elliott, 2003; Esposti & Valpiani, 2004). For instance, the long-term sequelae of poorly controlled hypertension include heart failure and kidney disease (Cushman, 2003). These complications subsequently increase health resource utilization (Zyczynski & Coyne, 2000). In 2006, the projected total cost of hypertension was 3% of the 2006 National Health Expenditure (Thom et al., 2006; Borger et al., 2006). Despite the availability of effective pharmacological treatments for hypertension, blood pressure still

remains poorly controlled in up to 66% of US patients (Elliott, 2003). Hypertension is therefore associated with substantial economic and human costs (Zyczynski & Coyne, 2000).

1.1.1 Problem statement

Inadequate adherence to prescribed medication may partly explain the problem of poor blood pressure control (Neutel & Smith, 2003). The factors predicting adherence to medication in hypertension and chronic disease are numerous (Fincham, 2005a). These factors include antihypertensive treatment attributes or characteristics such as efficacy, adverse events, out-of-pocket cost and dosage (Chen et al., 2005; Piette, Heisler, & Wagner, 2004). Although pharmacological treatment attributes impacting adherence in patients with hypertension have been identified and studied (Ogedegbe et al., 2004), patient choice or preferences for these treatment attributes are less well investigated (Bowling & Ebrahim, 2001).

The relative importance of antihypertensive treatment attributes, the effects of treatment attribute preferences on choice of antihypertensive treatment and the trade-offs that patients with hypertension make among treatment attributes, need to be more fully evaluated. The nature of patient preferences for antihypertensive therapy needs to be evaluated because, the inclusion of patient preferences in antihypertensive treatment decision making has the potential to improve adherence, enhance the likelihood of treatment success and to avoid additional resource utilization arising from the complications of chronic hypertension (Bernadini, 2004; Sokol et al., 2005). In addition, the monetary value placed by patients with hypertension, as determined by indirect willingness to pay, on increased levels of efficacy, simpler dosage regimens and lower

risk of adverse events associated with antihypertensive treatment is also not known. The current study will address this gap in the hypertension preference assessment literature using a discrete choice experiment (DCE).

The goal of this study therefore, is to examine the preferences of adult respondents as determined by patient choice, for the attributes or characteristics of antihypertensive treatment in a cost benefit analysis framework. The attributes include efficacy, risk of adverse events, out-of-pocket cost (co-payment) and dosage corresponding to the profile of the angiotensin-converting enzyme Inhibitors (ACEIs), an important class of antihypertensive medications.

The profile of the ACEIs was selected for this study for several reasons. The ACEIs are currently among the most widely prescribed antihypertensive medications in the US compared to the older drug classes such as the diuretics (Johnson & Singh, 2005). Furthermore, the ACEIs are effective as monotherapy in up to 70% of patients with stage one hypertension, the most prevalent presentation of hypertension (Ram 2002). Lastly, the ACE inhibitors provide important levels of target organ protection.

A discrete choice experiment will be performed utilizing the Georgia poll, a random digit dial [Groves et al., 1988] telephone survey of adults in the State of Georgia US, administered by the Survey Research Center (SRC), a component of the Office of Research Services at the University of Georgia. Participants in this study will be asked to assume they are hypertensive, regardless of their current hypertensive status.

1.1.2 The importance of consumer choice

Patient education and inclusion of patient preferences in antihypertensive treatment decision making has the potential to improve adherence (Osterberg &

Blaschke, 2005; Bernardini, 2004). Improved adherence can enhance treatment success, avoid complications and hospitalizations and consequently, produce substantial cost savings (Sokol et al., 2005). Therefore, consideration of the patient's perspective in antihypertensive treatment decision-making is important.

1.1.3 The epidemiological burden of cardiovascular disease

Cardiovascular disease is a highly prevalent public health challenge in the United States (Thom et al., 2006; Black, 2003). One in three adults in the US have one or more cardiovascular diseases, the most common including hypertension, coronary heart disease and stroke (Thom et al., 2006). Over 65 million Americans have hypertension and nearly 5 million Americans have heart failure (Thom et al., 2006). Therefore, cardiovascular disease remains a persistent and widespread problem in the US.

Cardiovascular disease is the leading cause of death among US adults (Ram & Vergne-Marini, 2004). Approximately 40% of all deaths in the US are due to cardiovascular disease (Black, 2003). Over 80% of cardiovascular disease-related deaths occur above the age of 65 years (Thom et al., 2006).

1.1.4 The economic burden of cardiovascular disease

Cardiovascular disease is associated with a significant economic burden in the US (Bonow et al., 2002). Cardiovascular disease-related disability leads to lost productivity and income for patients, employers and society (Hodgson & Cai, 2001). Patients with cardiovascular disease utilize more healthcare resources compared to non-patients (Paramore et al., 2001). Furthermore, the total cost for cardiovascular disease in the US for 2006 was projected to exceed $400 billion dollars or about 3% of the 2006 US Gross Domestic Product (Thom et al., 2006; Borger et al., 2006).

1.1.5 The epidemiological burden of hypertension

Hypertension presents a substantial epidemiological burden in the US (Nabel, 2003). One in three US adults has hypertension and the prevalence of hypertension increases with age (Fields et al., 2004; Hajjar & Kotchen, 2003). Hypertension is the most important risk factor for other cardiovascular diseases such as heart failure and kidney disease (Ram & Vergne-Marini, 2004). In addition, hypertension is responsible for about 5% of the cardiovascular disease-related deaths in the US (Thom et al., 2006). Similar to other cardiovascular diseases, hypertension is a significant cause of death and disability among US adults (Cushman, 2003).

1.1.6 The economic burden of hypertension

The total cost of hypertensive disease in 2006 was estimated to be $63.5 billion, of which about $24.4 billion will be spent on antihypertensive drugs (Thom et al., 2006). The average yearly expenditure per hypertensive patient increases with age and patients 75 years or older account for over 30% of the cost of hypertension (Hodgson & Cai, 2001).

1.2 Objectives of the study

This study has the following objectives:

1. What is the relative importance of the efficacy, adverse events, cost and dosage attributes of antihypertensive treatment in adult patients?
2. What are the effects of patient preferences for varying treatment attributes, trade-offs among treatment attributes and patient demographic characteristics (age, gender, ethnicity, education, income and metropolitan

statistical area) upon patient choice to purchase an ACE Inhibitor prescribed for hypertension?

1.3 Theoretical framework

Discrete choice experiments (DCEs) are based theoretically on Lancaster's economic theory of value (Lancaster, 1966; Ryan & Gerard, 2003). Lancaster's theory proposes that goods and services are composed of multiple attributes or characteristics of value to consumers. According to Lancaster (1966), consumers derive utility or value from the attributes of a good. Lancaster (1966) also proposed that combined goods might generate attributes, absent in either good separately. DCEs are attribute-based measures of preference or benefit (Ryan & Gerard, 2003). DCEs are premised on the basis of description of goods in terms of attributes and the assignment of preference based on the levels or range of values of these attributes (Ryan & Gerard, 2003). This study is consistent with Lancaster's theory of value because DCEs and Lancaster's theory both share a multi-attribute approach to the assessment of value.

Lancaster's theory has found application in various fields. Initially, it was applied in market research (Lancaster, 1966). Its subsequent applications include the analysis of consumer demand (Lancaster, 1971) and current applications include the measurement of patient preferences through discrete choice experiments (Ryan & Gerard, 2003).

Other theoretical frameworks are applicable to this study. These theories include, random utility theory, developed by McFadden (1986), which describes decision making under uncertainty. Statistical design theory is used to select profiles presented to participants (Ryan & Gerard, 2003; McFadden, 1986; Hanemann, 1984). Welfare

economic theory is the basis of willingness to pay and cost benefit analysis (McIntosh, Donaldson & Ryan, 1999). This study therefore employs several theoretical frameworks with Lancaster's theory serving as the primary theoretical foundation.

1.4 Survey and setting

1.4.1 The Georgia poll

The Georgia poll is a random digit dial telephone survey of adults 18 years or older in the State of Georgia, US, conducted by the Survey Research Center of the University of Georgia. The resulting data from each survey administration includes a standard set of demographic variables: gender, ethnicity, level of education, income, age and urban/rural status. In 2005, a study evaluating the factors affecting the likelihood of purchasing imported prescription drugs was completed using a discrete choice experiment framework and the random digit dial format of the Georgia poll (Fincham 2005b). Therefore, based on previous studies such as the Fincham 2005 study, the random digit dial telephone survey format of the Georgia poll and the discrete choice experiment framework are valid methods of obtaining stated preference data. The Fincham study provides further evidence that the discrete choice experiments can be successfully administered through telephone surveys.

1.4.2 Random digit dial surveys

Random digit dialing is a telephone sampling methodology that generates telephone numbers randomly from a frame of all possible telephone numbers in a defined sample domain (Lepkowski, 1988). The Georgia poll generates telephone numbers through stratified sampling, ensuring that a probability sample is extracted from land-based phones in the State of Georgia, United States. Adult residents of

households in the State of Georgia therefore have an equal or nearly equal probability of being selected as participants for this study (SRC, 2005). Because of the increasing use of cell phones and because the Georgia poll does not sample from cell phone subscribers, the Georgia poll may introduce a level of selection bias into the study. Respondents to the Georgia poll are those individuals who are at home while the Georgia poll is being administered. The exclusion of individuals with cell phones from this study may result in a homogenous population that may limit the external validity or generalizability of the current study.

1.5 Significance of research

This study is unique in several respects. First of all, this study was the first to evaluate patient preferences for the attributes of the ACEIs utilizing a discrete choice experiment. It is important to evaluate the preferences of patients for ACEI and antihypertensive therapy because the inclusion of patient preferences in treatment decision-making has the potential to improve adherence and enhance treatment success. Furthermore, this study evaluated, for the first time, the relative importance that patients associate with the various attributes of a specific class of antihypertensives (the ACEIs) and examined the trade offs that patients make among these attributes when they consider treatment acceptance. It is important to examine the choice to accept therapy because the choice of whether or not to accept a treatment is the first step towards compliance to antihypertensive therapy.

To the best of our knowledge, this study is the first to evaluate the monetary value or benefit, as determined by indirect willingness to pay, that patients place on improved efficacy, simpler dosage regimens and reduced risk of adverse events of a

specific class of antihypertensive treatment, the ACEIs. The current study obtained derived or indirect willingness to pay estimates for the improved levels of treatment attributes such as improved efficacy, improved side effect profile and improved dosage convenience. Respondents did not directly evaluate willingness to pay for improved levels of these treatment attributes.

The ratio of a treatment attribute coefficient and the cost attribute coefficient results in indirect willingness to pay estimates for improvement in the levels of the attribute under consideration. This study will make an important contribution to the extant preference assessment literature by using a discrete choice experiment to research patient preferences for the treatment of hypertension, a disease with enormous economic and public health impact.

CHAPTER TWO

LITERATURE REVIEW

2.1 Cardiovascular disease

Cardiovascular disease encompasses several distinct and yet inter-related disorders of the heart and vasculature system (Black, 2003; Wood & Kotseva, 2004). In the United States, the major cardiovascular diseases, based on prevalence and mortality data, are coronary heart disease, stroke, heart failure, hypertension, diseases of the arteries, congenital cardiovascular defects and rheumatic disorders (Thom et al., 2006; Cooper et al., 2000; Labarthe, 1998). In the last decade, these diseases have remained the most important cardiovascular disorders in terms of their epidemiological and economic impact on United States health care delivery and financing (Thom et al., 2006; Levy & Brink, 2005, Cooper et al., 2000; Smith, 1987; Labarthe, 1998).

2.1.1 The Burden of cardiovascular disease

Cardiovascular disease is responsible for a substantial epidemiological and economic burden in the United States (Thom et al., 2006; Black, 2003). Approximately 70 million Americans have one or more cardiovascular diseases (Thom et al., 2006). Cardiovascular disease is the leading cause of death among US adults (Ram & Vergne-Marini, 2004). Approximately 40% of all deaths in the US are due to cardiovascular diseases (Black, 2003). The total cost for cardiovascular diseases in the US for 2006 was projected to exceed $400 billion dollars (Thom et al., 2006).

Hypertension presents a substantial epidemiological burden to the United States health care system (Nabel, 2003). For instance, one in three US adults has hypertension and the prevalence of hypertension increases with age (Fields et al., 2004; Hajjar & Kotchen, 2003). Furthermore, hypertension is the most important risk factor for other cardiovascular diseases such as heart failure and kidney disease (Ram & Vergne-Marini, 2004).

2.1.1.1 Congestive heart failure

Hypertension is a known risk factor for congestive heart failure (CHF) [Ram & Vergne-Marini, 2004; Masoudi et al, 2002]. In 2003, about 5 million people had heart failure and 550,000 new cases are expected annually (Thom et al., 2006). The prevalence of CHF increases with age (Masoudi et al, 2002). The total cost of CHF in 2006 was projected to be $29.6 billion (Thom et al., 2006). The prognosis of heart failure is poor. It is expected that 80% of men and 70% of women with heart failure under the age of 65 years will die within 8 years (Thom et al., 2006). Unlike other cardiovascular diseases, the prevalence and incidence of heart failure is on the increase. Patients with CHF make greater than 11 million physician office visits annually and there are 3.5 million hospitalizations for CHF every year. Readmission rates are also very high in CHF and as much 50% of CHF patients discharged are expected to be re-hospitalized within 6 months of discharge (Bungard, et al, 2001).

2.1.1.2 Kidney failure

Kidney failure or end-stage renal disease occurs when the kidneys are no longer able to function (Manley & Carroll, 2002). When the kidneys fail, patients are required to have regular kidney dialyses or to receive a kidney transplant (Eknoyan et al., 2004). In

2003, over 100,000 cases of end-stage renal disease were reported. About 82,588 individuals died of kidney failure in 2003. The most common cause of kidney failure is diabetes (Thom et al., 2006). However, hypertension is another risk factor strongly associated with the development of kidney failure (Thom et al., 2006).

2.1.2 Economic and health system impact of hypertension

The cost-of-illness due to hypertension in the United States is enormous (Hodgson & Cai, 2001). The total cost of hypertensive disease in 2006 was estimated to be $63.5 billion, of which about $24.4 billion will be spent on antihypertensive drugs (Thom et al., 2006). The average yearly expenditure per hypertensive patient increases with age and patients 75 years or older account for over 30% of the cost of hypertension (Hodgson & Cai, 2001). The complications of hypertension such as heart failure and kidney failure may subsequently increase health resource utilization (Paramore et al., 2001; Zyczynski & Coyne, 2000). Despite the availability of effective pharmacological treatments for hypertension, blood pressure still remains poorly controlled in up to 66% of patients in the United States (Elliot, 2003).

2.1.3 Impediments to the optimal treatment and control of hypertension

The goal of antihypertensive therapy is to lower blood pressure to normal levels and to prevent or reverse the complications of hypertension such as heart and kidney failure (Neutel & Smith, 2003; Sica, 2003; Cushman, 2003). Hypertension is poorly controlled in a majority of patients (Sica, 2003). In the United States, nearly 70% of treated hypertensive patients have their blood pressure inadequately controlled (Elliot, 2003; Zyczynski & Coyne, 2000). The problem of poor blood pressure control may be exacerbated by sub-optimal adherence to antihypertensive therapy (Zyczynski & Coyne,

2000). Adherence has been defined generally as the degree to which a person's behavior coincides with medical advice or recommendations (Haynes, 1976).

2.2 Factors related to adherence with antihypertensive treatment

The factors that determine blood pressure control and adherence to therapy are numerous and have been researched extensively (Lindholm, 2002; Vidt, 2002). These determinants include physician-related, treatment-related and patient characteristics or sociodemographic factors (Lindholm, 2002; Vidt, 2002; Haynes, 1976,). For instance, a lack of aggressive management of hypertension on the part of some physicians may worsen the problem of poor blood pressure control (Neutel & Smith, 2003; Oliveria et al., 2002; Lindholm, 2002). Other physician-related factors that may be responsible for poor adherence to antihypertensive treatment includes a focus on diastolic blood pressure as the sole measure of the degree of blood pressure control despite current evidence that systolic blood pressure is a strong and independent predictor of the risk of cardiovascular events especially in elderly hypertensive patients (Oliveria et al., 2002; Lindholm, 2002).

The attributes of the prescribed medications themselves may determine the levels of blood pressure control and adherence to antihypertensive therapy (Neutel & Smith, 2003). The attributes of antihypertensive therapy that have been associated with adherence include the adverse event profiles of antihypertensive treatments, the efficacy of treatment, dosage schedule and the cost of therapy (Ogedegbe, et al 2004; Salman et al., 1999; Neutel & Smith, 2003; Piette, et al, 2004; Zyczynski & Coyne, 2000; Lindholm, 2002; Dusing et al., 1998; Rice & Matsuoka, 2004; Sanson-Fisher & Klover, 1995).

Studies examining the association between age, gender, ethnicity, income, education and geographical location and adherence to therapy in hypertension as well as other diseases have been equivocal (Haynes, 1976). Several studies suggest that these sociodemographic factors are associated with adherence either alone or in combination with other factors (Weingarten & Cannon, 1998; Morris et al., 2006; Haynes, 1976; Wilson & Ampey-Thornhill, 2001; Waeber, 2001; Taira, et al, 2006). Other studies have shown no association between patient sociodemographic factors and adherence (Haynes, 1976; Davis & Eichhorn, 1963; Donabedian & Rosenfeld, 1964; Heinzelmann, 1962; Finnerty, et al, 1973; Moulding, et al., 1970).

The lack of consistent findings in the association or otherwise of sociodemographic factors and adherence may be due to several factors. For instance, differences may exist across studies in the definitions offered for adherence. Also, the variability in the association of sociodemographic factors and adherence could also be due to different sample sizes used in different studies. Other causes of inconsistent findings may include the type of population sampled, the degree of heterogeneity of the sample and the way in which adherence was measured across different studies. Lastly, the degree of internal and external validity of the study and the outcome measures and instruments selected to measure adherence all have the potential to impact reported adherence levels.

The determinants of adherence to treatment for hypertension as well as other chronic diseases have been well investigated (Haynes, 1976; Lindholm, 2002; Vidt, 2002). However, there appears to be a need to further examine the impact of treatment

attributes and sociodemographic factors on patient antihypertensive treatment preferences, as defined by patient treatment choice.

Researching the nature of patient preferences for antihypertensive therapy, especially the determinants of patient treatment choice for antihypertensive therapy is important for various reasons. First of all, the knowledge of the determinants of patient treatment choice will add to the extant hypertension preference assessment literature by determining whether or not patients are willing to participate in antihypertensive treatment decision making if adequate information is provided to them about the attributes of treatment such as the efficacy, side effects, dosage schedule and the cost of therapy. Secondly, knowledge of the relative importance ascribed to the attributes of the ACEIs as well as other antihypertensive agents will be useful to clinicians by identifying concerns that are most important to patients in various population subgroups. Physicians and other clinicians may therefore have a basis for prioritizing the information presented to patients when the consultation time between patients and physicians is limited. Thirdly, knowledge of the value placed on the different attributes of antihypertensive therapy is important because goods, services, healthcare interventions and treatments, are composed of different attributes. These attributes make different contributions to the final value ascribed to the product and a multi-attribute preference measurement approach such as a discrete choice experiment can reveal the relative importance that patients ascribe to the different attributes of the treatment such as the ACEIs as well as other antihypertensive agents. The relative contributions that these treatment attributes make to the final value ascribed to the ACEIs may thus be determined using a discrete choice experiment.

The employment of a discrete choice experiment provides two important measures of patient preferences: utilities and monetary estimates of indirect willingness to pay for the attributes of ACEI and other antihypertensive therapy. This is in contrast to direct willingness to pay elicitation that yields only monetary estimates of strength of preference. Therefore, the application of a discrete choice experiment provides a useful tool to further understand the nature of patient preferences for ACEI therapy.

The relationship between the attributes of treatment, patient characteristics and patient treatment choice, as well as patient treatment preferences, has been reported across several diseases including breast cancer (Pusic et al., 1999), benign prostatic hyperplasia (Kaplan, et al., 1995; Watson et al., 2004), epilepsy (Brodie & Kwan, 2001; Lloyd, et al., 2005) and myopia (Gupta & Naroo, 2006).

The reports investigating patient preferences and treatment choice have used disease-specific and evidence-based treatment guidelines, recommendations, drug formularies and empirical methods to examine the factors that determine treatment choice (Brodie & Kwan, 2001; Alexander, 2006; Weekes & Day, 1998; Say, et al., 2006). While treatment guidelines provide an important foundation upon which to base treatment-related decisions, these guidelines do not always consider patient preferences for treatment. Empirical studies have used contingency tables, correlations and regression methods, including logistic regression, discrete choice experiments (DCEs) and conjoint analysis to determine the relationship between treatment-related factors, patient characteristics and patient treatment choice (Pusic et al., 1999; Gupta & Naroo, 2006; Ryan, 1999; Lloyd et al., 2005; Watson et al., 2004; Hundley & Ryan, 2004; Say, et al., 2006).

A search of the literature did not reveal a study reporting the relationship between the attributes of antihypertensive therapy, patient characteristics and patient treatment choice using a discrete choice experiment. Although preferences for antihypertensive therapy has been determined using qualitative approaches and willingness to pay studies, these studies did not employ the profiles of specific antihypertensive agents such as the ACEIs and only examined the generic profiles of antihypertensive agents (Ogedegbe et al, 2004; Johannesson et al, 1991). In addition, the willingness to pay studies obtained holistic or aggregate estimates of monetary value for non-specific antihypertensive agents and did not assess the monetary value attached by patients to the improvement in the levels of the particular attributes of antihypertensive therapy such as higher levels of efficacy, lower risk of side effects and more convenient dosage regimes.

The current study will fill a gap in the extant hypertension preference assessment literature by employing a discrete choice experiment to determine the nature of patient preferences for antihypertensive therapy for a specific class of antihypertensive agents; the ACEIs, unlike previous studies. Furthermore, indirect willingness to pay estimates for improvement in the levels of treatment attributes may be obtained from a marginal rate of substitution analysis and a discrete choice experiment. This study is unique because it is the first to assess the relative importance of ACEI treatment attributes using a discrete choice experiment. This study is also the first to generate willingness to pay estimates for improvements in the levels of the attributes of the ACEIs. The willingness to pay estimates obtained from this study may also be incorporated into a future cost benefit analysis.

The discrete choice experiment has been gaining increasing use in the preference assessment literature and has been applied in other chronic diseases such as benign prostatic hyperplasia (Ryan & Gerard, 2003; Watson et al., 2004). The absence of a discrete choice experiment in the assessment of patient preferences and treatment choice for antihypertensive therapy may be due to the relatively recent introduction of discrete choice experiments into health preference assessment. Therefore, this study makes an important contribution to the hypertension preference assessment literature by using a discrete choice experiment to research patient preferences for the treatment of hypertension, a disease with enormous economic and public health impact. This study also successfully employed a telephone survey adapted discrete choice experiment to address the research objectives outlined in chapter 3, making it one of only a few studies that have employed a telephone adapted discrete choice experiment in the assessment of patient preferences. The discrete choice experiment provides the relative importance of treatment attributes as well as indirect willingness to pay estimates for improvement in the levels of ACEI attributes.

2.3 Patient preferences for antihypertensive therapy

Preference measurement refers to the expression of value for alternative options for health interventions such as drugs after consideration of the risks and benefits associated with the health interventions (Bowling & Ebrahim, 2001). Information on the risks and benefits associated with the attributes of alternative antihypertensive treatments may be presented to patients by clinicians in the context of a clinical consultation in the process of treatment decision making using language that the patients can understand. In the chronic disease preference assessment literature,

patient preferences have been assessed by the levels of patient involvement in medical or treatment decision making, patient treatment choice and willingness to pay using health surveys, discrete choice experiments, qualitative methods and contingent valuation surveys (Ratcliffe, et al., 2004; Petrou & Henderson, 2003; Lloyd, et al., 2005; Diener, et al., 1998; Neumann and Johannesson, 1994; Whittington et al., 2002).

The measurement of patient preferences determines what interventions or attributes of interventions drive patient preferences and need to be provided in increasing amounts in the context of health policy and clinical decision making (Bowling & Ebrahim, 2001; Neuman, et al., 2000). In the case of antihypertensive treatment, this study identified, using a DCE, how ACEI treatment attributes such as efficacy, adverse event profile, dosage schedule and cost, influence patient preferences as determined by patient antihypertensive treatment choice. The relative importance of these treatment attributes was examined including the trade-offs that patient's make among the attributes of the ACEIs.

Not all patients wish to or are able to participate in treatment decision making. For patients who desire to participate in treatment decision-making, the measurement of patient preferences may significantly improve adherence. Other beneficial health outcomes include improved efficacy and a reduced risk of side effects. In the case of hypertension, improved adherence may attenuate the occurrence of cardiovascular events such as congestive heart failure and kidney failure.

2.3.1 Criticisms of preference measurement

The criticisms against the elicitation of patient preferences have centered on the practicality of preference measurement in the context of the physician-patient

interaction. For instance, the following challenges with preference measurement have been identified: the impact on physician consultation time (Say & Thompson, 2003) and a need for certain communication skills that the physician may not currently possess. Other perceived barriers include the reality that not all patients desire to participate in treatment decision making, the challenges associated with the best ways to present risk and other kinds of information to patients, the availability of alternative sources of information such as the internet and a lack of congruence between the treatment preferences of physicians and patients (Say & Thompson, 2003).

Other authors have suggested that some of the perceived challenges associated with the elicitation and incorporation of patient preferences into clinical treatment decision-making may be overcome. For instance, Greenfield, Kaplan & Ware (1985) indicate that elicitation of patient treatment preferences did not unnecessarily disrupt the physician-patient interaction. Elwyn and colleagues (1999) indicate that physicians were willing to receive further training on how best to involve patients in treatment decision-making. Bowling and Ebrahim (2001) assert that a majority of patients want their physicians to understand their preferences even if they (patients) may not desire to make the final treatment decision.

While treatment factors impacting adherence to antihypertensive therapy have been identified and studied, the effect of treatment factors on patient preferences as determined by patient treatment choice, for a specific class of antihypertensive agent such as the ACEIs, is currently unknown. The focus of this study was to employ a discrete choice experiment to examine the relationship between antihypertensive treatment attributes, patient characteristics and patient choice of antihypertensive

therapy. A discrete choice experiment is able to employ a multi-attribute approach to determine the relative importance of ACEI treatment attributes as well determine indirect willingness to pay for improvements in the levels of ACEI treatment attributes.

2.3.2 Factors influencing patient preferences and treatment choice

Factors associated with patient preferences for participation in treatment decision making include sociodemographic variables or patient characteristics, the variables related to the experience of illness and health care, the attributes of treatment, the type of health decision, the information preferences of patients and disease severity (Say, et al., 2006; Arora & McHorney, 2000).

2.3.2.1 Sociodemographic variables

The influence of sociodemographic variables or patient characteristics such as age, race or ethnicity, income, education, gender and urban/rural location has been investigated in the preference assessment literature (Say, et al., 2006; Arora & McHorney, 2000). While the determinants of patient treatment preferences and treatment choice in cancer as well as other chronic diseases (Beaver et al., 1996; Hack, et al,, 1994; Salkeld, et al., 2005) have been well researched, there appears to be a need to further research the determinants of patient treatment choice, including sociodemographic variables, for antihypertensive therapy.

It is important to research the determinants of patient treatment choice in hypertension using a discrete choice experiment because this has not been investigated prior to the current study. Hypertension is an important chronic disease with long-term consequences. The determinants of patient treatment choice have been determined in other chronic diseases such as HIV and benign prostatic hyperplasia. Because of its

economic, epidemiological and social importance, there is a need to also examine the determinants of patient treatment choice in hypertension.

2.3.2.1.1 Age

The association between age and patient preferences has been examined in the preference assessment literature (Say, et al, 2006; Arora & McHorney, 2000). A majority of these studies indicate that age is negatively associated with patient preferences for treatment decision-making, with younger patients preferring a more active role in treatment decision-making compared to older patients (Say, et al., 2006; Degner & Sloan, 1992; Ende, et al., 1989; Stiggelbout & Kiebert, 1997; McKinstry, 2000). These studies were conducted in a variety of patients with chronic disease such as breast cancer (Beaver et al., 1996; Hack, et al., 1994), benign prostatic hyperplasia (Nease & Brooks, 1995) and asthma (Adams, et al., 2001). On the other hand, other studies indicate that age is not associated with patient preferences (Marshall, et al., 2006; Duric & Stockler, 2001). The association between age and patient preferences is therefore associated with some ambiguity.

The ambiguity associated with age and patient preferences for treatment decision-making may be attributed to the specific ways in which studies were completed. For instance, Degner and Sloan (1992) elicited preferences from cancer patients without making an attempt to control for the stage of cancer at which preferences were measured. Preferences in this study were also measured using a dichotomous outcome measure rather than as a continuous variable. The type of treatment the patient was taking was also not controlled for in this study. On the other hand, Duric and Stockler (2001) suggested that age was not associated with patient

preferences for treatment in early breast cancer. Their results may have been due to the nature or type of the cancer, the type of treatment offered and the population sampled. Therefore, even among studies obtaining patient preferences in a particular chronic disease, the stage, type and severity of the disease may determine whether or not age is associated with patient preferences for treatment decision making.

2.3.2.1.2 Ethnicity

The literature on the association between ethnicity and patient preferences suggests that white patients are more active in treatment decision-making compared to African American patients (Say, et al., 2006). Strull, Lo and Charles (1984), using a sample of hypertensive outpatients, suggested that ethnicity is associated with participation in treatment decision-making. Bosworth and colleagues (2006) indicate that compared to hypertensive white patients, hypertensive African American patients were more likely to have a lower level of literacy compared with white hypertensive patients which may further explain the lower propensity for participation in treatment decision making observed among African Americans. Strull and colleagues (1984) indicate the existence of ethnic disparity regarding participation in treatment decision-making. However, the influence of ethnicity on patient preferences is less well researched compared to the influence of the other patient characteristics on patient preferences for treatment decision making.

2.3.2.1.3 Gender

Various studies have reported an association between gender and patient preferences for decision making (Arora & McHorney, 2000). Blanchard and colleagues (1988) showed that gender was associated with treatment decision-making in a

population of cancer inpatients. Stiggelbout and Kiebert (1997) suggest that gender was associated with treatment decision-making in a sample of radiotherapy and surgical outpatients and their companions. These studies suggest that being female is associated with a higher likelihood of participation in treatment decision-making. Other studies have supported the association between gender and patient preferences (Degner & Sloan, 1992; Nease & Brooks, 1995). However, Yellen and Cella (1995) did not find an association between gender and patient preferences in cancer patients. The relationship between gender and patient preferences for treatment decision-making is therefore associated with some uncertainty. Degner and Sloan (1992) used a sample of patients with cancer while Yellen and Cella (1995) also used a sample of patients with cancer but assessed the influence of social factors such as social support on patient preferences for treatment decision making. The context in which the study is conducted therefore influences the results of the study.

2.3.2.1.4 Income

Various reports support an association between income and patient preferences for treatment decision-making. Ende and colleagues (1989) and Nease and Brooks (1995) suggest that income is a determinant of patient preferences. Other studies support the association between income and patient treatment decision making (Strull, et al., 1984; McKinstry, 2000; Beaver et al., 1996). These studies indicate that individuals with lower incomes are less likely to participate in treatment decision-making compared to individuals with higher incomes. While a majority of studies examining the influence of income on patient preferences for decision-making have found an association between the two concepts, a few studies did not find an association

between income and patient preferences for decision making (Bruera, et al., 2002; Wright, et al., 1994). Therefore, the association between income and patient preferences for treatment decision-making may be context-specific.

2.3.2.1.5 Education

Education has been shown to be a determinant of patient preferences. The trend suggests that individuals with lower educational levels are less active in treatment decision making (Say et al., 2006). Degner and Sloan (1992) found an association between education and patient preferences for treatment decision-making in patients with cancer. Furthermore, Adams and colleagues (2001) showed that an association exists between education and patient treatment preferences in asthmatic patients. Other studies also suggest the existence of an association between education and patient treatment preferences (Beaver et al., 1996; Ende, et al., 1989; Thompson, et al., 1993; Cassileth, et al., 1980; McKinstry, 2000). However, other studies suggest that there is no association between education and patient preferences for treatment decision-making. Bruera and colleagues (2002) did not find an association between education and patient preferences for treatment decision-making in a population of breast cancer patients. Similarly, Wright et al (1994) did not find an association between education and patient preferences for decision-making in patients with cervical cancer. Therefore, the relationship between education and patient preferences for decision-making is unclear and may be dependent on the particular research context.

2.3.2.1.6 Geographical location

Geographical location may be defined in terms of urban and rural area classification or metropolitan statistical area (MSA) and non-metropolitan statistical area

(Non-MSA) classification (Haynes et al., 1979; Zimmerman, 1968). MSAs are based on urban counties and represent contiguous areas of relatively high population densities (Zimmerman, 1968). The influence of geographical location on patient preferences has been reported in only very few studies. Anell and colleagues (1997) show that living in an urban area was associated with being more actively involved in treatment decision-making compared to living in a rural area. Although studies have shown the impact of geographical location on patient preferences, the literature in this area is not expansive.

2.3.2.2 Severity of the health condition

Studies across different disease categories have shown that the severity of the health condition may determine treatment decision-making in patients. Several studies indicate that patients with more severe illness may have a lesser propensity for involvement in treatment decision making compared to other patients with less severe illness (Say, et al., 2006; Blanchard, et al, 1988). Catalan and colleagues (1994) found that HIV patients with symptoms were less likely to prefer an active role in treatment decision-making compared to HIV patients without symptoms. Similarly, other studies suggest that patients with more severe disease were less likely to participate actively in treatment decision making compared to other groups of patients with less severe disease (Beaver et al., 1996; Arora & McHorney, 2000). On the other hand, Stewart and colleagues (2000) suggest that women with severe ovarian cancer were more likely to prefer a more active role in treatment decision making, compared to women with less severe ovarian cancer. Therefore, the severity of disease may influence patient preferences for treatment decision-making. The strength and direction of patient treatment preferences appears to be determined by the disease under consideration.

The impact of the severity of hypertension on patient preferences for treatment decision-making needs to be evaluated in future studies.

2.3.2.3 The nature of the health decision

The magnitude of the health decision may also influence patient preferences (Say, et al., 2006). Patients are more likely to prefer a more active role when they are confronted with a minor illness such as an upper respiratory infection (Ende, et al., 1989; Nease & Brooks, 1995). Patients with more serious illnesses such as severe exacerbations of asthma and benign prostatic hyperplasia have been shown to prefer a less active role in treatment decision making (Gibson, et al., 1995; Adams, et al., 2001; Ende, et al., 1989; Nease & Brooks, 1995).

2.3.2.4 Information seeking preferences

The relationship between information seeking preferences and patient preferences for decision-making has been examined. Patients with a greater desire for more information about their disease may prefer a more active role in decision-making compared to patients without a strong desire for information (Cassileth, et al., 1980; Sutherland et al., 1989). Information seeking behavior has been associated with having a stronger self-efficacy and stronger coping skills, which was also found to be associated with preference for involvement in treatment decision making (Arora & McHorney, 2000; Adams, et al., 2001).

2.3.2.5 Experience with illness

Several studies indicate that having an experience of illness may affect patient preferences for involvement in decision-making. Some studies have shown that experience with an illness was associated with a decreased preference for involvement

in treatment decision-making. Degner and Sloan (1997) found that newly diagnosed cancer patients were less likely to take an active role in treatment decision-making compared to persons without cancer. Other studies suggest that experience with an illness was associated with a diminished preference for treatment decision making (Stiggelbout & Kiebert, 1997; Thompson, et al., 1993). On the other hand, other studies indicate that a temporal relationship exists between patient treatment preferences and the experience of illness (Mansell, et al., 2000; Butow, et al., 1997; Degner et al., 1997).

2.3.2.6 Experience with healthcare

Experience with healthcare and health professionals is associated with preferences for treatment decision-making. Adams and others (2001) found that patients who perceive that their physicians were willing to involve patients in treatment decision-making were more apt to desire a more active role in expressing their treatment preferences. Blanchard and colleagues (1988) identified physician behaviors that were associated with a greater desire to participate in treatment decision making for cancer patients. These characteristics included the responsiveness of the physician to the patient's verbal and nonverbal behaviors and the physician's assessment of prognosis. Congruence between the treatment approach of the physician and the patient's treatment preferences may improve adherence and long-term health outcomes (Bernardini, 2004).

2.3.2.7 Treatment attributes and patient treatment choice

Patient preferences for the characteristics of treatments for acute and chronic disease are important because of the impact of these preferences on adherence as well as other health outcomes (Bowling & Ebrahim, 2001). Consideration of patient

preferences for therapy may also avoid long term costs of therapy due to worsening disease severity or development of complications by identifying factors driving patient preferences and providing more of these important attributes in order of relative importance (Neumann, et al., 2000; Sokol et al., 2005).

The literature on the effects of treatment attributes on patient choice of therapy is centered on the use of discrete choice experiments and conjoint analysis in various disease scenarios. Discrete choice experiments have the distinct advantage of being able to value the attributes of treatment and the effect of these attributes on patient choice (Ryan & Gerard, 2003). Treatment characteristics that have been examined across different disease areas include efficacy attributes, adverse event attributes, dosage schedule and cost of therapy (Sherer et al., 2005; Beusterien et al., 2005; Ashcroft, et al., 2006; Mantovani et al., 2005; Lloyd, et al., 2005). Some non-health outcome attributes or process attributes that have been examined in the literature include extent of healthcare practitioner involvement and healthcare practitioner communication style (Hundley, et al., 2001; Hundley & Ryan, 2004).

The literature on the effects of treatment attributes on patient choice using discrete choice experiments is growing and appears to be disease and context specific. While considerable work has been done in several areas in order to determine the relative importance of treatment attributes and patient choice of therapy in chronic diseases like HIV and benign prostate hyperplasia (Beusterien et al., 2005; Watson et al., 2004), the literature suggests a dearth of research delving into the nature of the relationship between treatment attributes and patient treatment choice, measured using a DCE, in the hypertension preference assessment literature. Therefore, the current

study examined the effect of treatment attributes such as efficacy, adverse event profile, dosage schedule and the cost of antihypertensive therapy on patient treatment choice.

The current study used a discrete choice experiment in the context of patient preferences for a specific class of antihypertensive agents, the ACEIs. DCEs have been used successfully to measure preferences in other chronic diseases such as HIV and the successful application of a discrete choice experiment to assess preferences for antihypertensive therapy provides further evidence of the validity of the technique.

The disease condition determines the definition offered for the efficacy, adverse event, dosage schedule, cost and other attributes of treatments and interventions under consideration. In the HIV preference assessment literature, efficacy has been conceptualized as the ability of therapies to lower HIV viral load, the ability of therapies to increase CD4 cell counts and the ability of therapies to retard the development of viral resistance to the medication (Sherer et al., 2005; Beusterien et al., 2005). In epilepsy, efficacy has been defined in terms of seizure control (Lloyd, et al., 2005). In benign prostate hyperplasia, treatment efficacy has been defined as the ability to reduce the size of the prostate and time to improvement of symptoms (Watson et al., 2004). Similarly, the definitions offered for the adverse events and other attributes of treatment are also disease-specific (Ashcroft, et al., 2006; Mantovani et al., 2005).

2.3.2.7.1 Efficacy

Although efficacy has been defined in different ways based on the disease or therapeutic area, efficacy is positively associated with patient treatment choice. HIV treatment efficacy was positively associated with treatment choice (Sherer et al., 2005). Similarly, efficacy of treatment against benign prostate hyperplasia was also a

significant positive predictor of patient choice (Watson et al., 2004). Other studies have shown a positive association between efficacy or benefit attributes and treatment choice (Lloyd, et al., 2005; Hundley, et al., 2001; Hundley & Ryan, 2004). The relationship between efficacy variables and treatment choice therefore, appears to be consistent.

2.3.2.7.2 Adverse event profile

Various studies describe the relationship between adverse events and treatment choice. Ashcroft, Seston and Griffiths (2006) investigated the influence of attributes of treatment for psoriasis including adverse event attributes on patient treatment choice. In this study, adverse events were defined in terms of the risk of skin irritation, 20 year risk of liver damage and 20 year risk of skin cancer. These attributes were found to be significant negative predictors of patient choice. Furthermore, Lloyd, McIntosh and Price (2005) also found a negative relationship between adverse events such as weight gain, and patient choice of therapy in epilepsy. These studies suggest that as the risk of adverse events increases, the likelihood of patients selecting treatment decreases (Watson, et al., 2004; Ratcliffe et al., 2004).

2.3.2.7.3 Dosage schedule

Studies of the influence of dosage schedule on patient treatment choice shows that the likelihood of patient treatment choice decreases with increasing complexity of the dosage schedule. Beusterien et al (2005) showed that the dosage schedule of medications against HIV was negatively associated with patient treatment choice. Sherer and colleagues (2005) showed that dosage schedule was negatively associated with patient treatment choice in a sample of HIV patients. Mantovani and colleagues (2005) showed that the dosage frequency of treatment products for hemophilia was

negatively associated with treatment choice. Therefore, the studies of the influence of dosage schedule on patient treatment choice appear to be consistent and suggest that a negative relationship exists between dosage schedule complexity and treatment choice.

2.3.2.7.4 Cost of therapy

The effect of the cost of therapy on patient choice has been studied. Aristides and colleagues (2004) showed that cost of therapy of diabetes was negatively associated with the likelihood of treatment choice. Similarly, Lloyd, McIntosh and Price (2005) also found a negative relationship between the cost of epilepsy treatment and the likelihood of patient choice of treatment. Watson and colleagues (2004) also found a negative relationship between cost of therapy for benign prostate hyperplasia and patient treatment choice. Other studies have found a negative relationship between the cost attribute and patient treatment choice (Phillips, et al,, 2002; Ryan & Hughes, 1997; Ryan, 1999; Taylor & Armour, 2003). The literature on the relationship between cost of therapy and patient choice therefore appears to be consistent and suggests that a negative relationship exists between cost and treatment choice.

In summary, the relationship between patient sociodemographic variables or patient characteristics, treatment attributes as well as other variables and patient preferences has been studied across several diseases. These diseases include cancer, asthma, benign prostate hyperplasia and epilepsy, using a variety of techniques such as health surveys, DCEs, conjoint analysis and qualitative methods. There appears to be a dearth of studies assessing patient preferences for antihypertensive therapy. No DCE assessing the impact of patient characteristics and antihypertensive treatment attributes

on patient choice of therapy was found in the literature. This may be due to the relatively novel utility of the discrete choice approach in health economics. The current study addressed this gap by examining the impact of patient characteristics and treatment attributes on patient preferences as determined by patient treatment choice and measured by a DCE.

2.4 Guidelines for the treatment of hypertension

There are several guidelines in existence recommending various treatment approaches for hypertension (Weir, 1991; Thakkar & Oparil, 2001). An important guideline for the treatment of hypertension is the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [Moser, 2006]. Other commonly cited guidelines include the World Health Organization and International society for Hypertension guidelines (WHO-ISH), the British Hypertension Society (BHS) and the European Society for Hypertension/ European Society for Cardiology guidelines (ESH-ESC) [Moser, 2006; Thakkar & Oparil, 2001; Mancia & Grassi, 2005; Carter, 2004].

2.4.1 Stepped care therapy

In an effort to streamline physician prescribing practices, the National Heart, Lung and Blood Institute (NHLBI) convened the first Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC) in 1977 (Poulter, 1991). The first JNC report presented the ‘stepped care’ therapy approach to the management of hypertension (Saunders, 1986). The stepped care approach has witnessed various changes over the past 30 years, as new antihypertensive drug classes have become available (Moser, 2006).

The first JNC report approach to stepped care therapy suggested commencing therapy for hypertensive patients using a low dose of a thiazide diuretic as the first step (Weir, 1991; Poulter, 1991; DeQuattro, 1990). If blood pressure was inadequately controlled after dose titration, combination therapy with a second drug from a different class was recommended. If a two drug combination was not successful in controlling blood pressure, a third drug may be added. The fourth and final step of the stepped care approach involved the addition of guanethidine as the fourth drug or replacing the agents at step two with guanethidine (Moser, 2006).

The second JNC report, published in 1980 (Krishan & Moser, 1980) differed from the first report primarily with the availability of other beta-blockers which may be used in place of propranolol at step two. The third JNC report (JNC III) was published in 1984 (DeQuattro, 1990; Moser, 2006). The committee suggested in JNC III that beta-blockers might be used as an alternative to a thiazide diuretic in step one. The subsequent steps of JNC III are similar to those of the 1980 report (DeQuattro, 1990).

In 1988, newer classes of antihypertensive agents such as the angiotensin converting enzyme Inhibitors and the calcium antagonists had become available (Chobanian et al., 2003; Moser, 2006). Similar to the 1980 report, the fourth report of the JNC suggested that the first step include monotherapy with any one of four classes of antihypertensives (diuretics, calcium antagonists, beta blockers and angiotensin converting enzyme inhibitors [ACEIs]). The committee recommended the individualization of antihypertensive therapy for each patient at this point with the careful consideration of patient characteristics before the treatment decision is made (Chobanian et al., 2003).

The fifth JNC report was published in 1993 (Miller & Jehn, 2004). The report offered a new classification system for hypertension consisting of four stages based on severity. Stage one hypertension was defined as systolic and diastolic blood pressure readings of 140-159/90-99 mmHg (Moser, 2006; Miller & Jehn, 2004). Stage two hypertension is defined as blood pressure levels of 160-179/100-109 mmHg. Stage three hypertension is characterized as blood pressure levels of 180-209/110-119 mmHg and stage four hypertension is characterized as blood pressure levels of 210/120 mmHg or higher (Miller & Jehn, 2004).

In 1997, the sixth report of the JNC included several changes such as a more diverse set of recommendations on lifestyle modification as therapy against hypertension (non-pharmacological management of hypertension) [Sheps, 1999; Miller & Jehn, 2004]. JNC 6 classified blood pressure in two new ways; risk stratification and staging. The changes in blood pressure classification were to enable the identification of high-risk individuals. Stages 3 and 4 in JNC 5 were merged together as stage 3 in JNC 6 (Sheps, 1999).

The current JNC report is JNC 7, which was published in 2003 (Chobanian et al., 2003; Alderman, 2004). JNC 7 established a new classification category called 'prehypertension'. Individuals who are prehypertensive have blood pressure levels of 120-139/80-89 mmHg. About 60 million American adults fall into this category. Antihypertensive therapy may be beneficial in prehypertensive individuals but possible benefits have not been shown. However, lifestyle modification may benefit these persons and may prevent the eventual development of hypertension (Miller & Jehn, 2005; Chobanian et al., 2003).

Since the presentation of the first JNC report, the nature of the stepped care therapy approach has changed with the introduction of newer classes of antihypertensive agents (Moser, 2006). However, individualized therapy has largely substituted stepped care therapy (Weir, 1991; Saunders, 1986; Taylor, 1990) because of the various factors unique to each individual such as renin status, patient demographic characteristics and socioeconomic status that should be considered before choosing a treatment alternative (Weir, 1991; Laragh, 1984; Saunders, 1986; Moser, 2006).

2.5 Available therapies

Hypertension is usually treated using a combination of non-pharmacological and pharmacological treatments (Wexler & Aukerman, 2006; Wood & Kotseva, 2004). Non-pharmacological treatment is also referred to as lifestyle modification and is usually the first step in the management of the hypertensive patient (Wexler & Aukerman, 2006). Patients who are not well controlled with lifestyle modification may commence therapy with pharmacological agents such as the diuretics, angiotensin converting enzyme inhibitors and the calcium antagonists (Ram, 2002).

2.5.1 Lifestyle modification

Lifestyle modification refers to the non-pharmacological interventions such as smoking cessation, regular exercise, weight loss, low-fat, low-salt diets and limiting excessive alcohol consumption (Beilin et al., 2001; Wexler & Aukerman, 2006). Lifestyle modification is usually attempted before the patient is placed on antihypertensive medication and hypertensive patients are encouraged to adhere to lifestyle modification even when medication has been prescribed (Beilin et al., 2001).

There are several options for the pharmacological management of hypertension (Ram, 2002). These options include: diuretics, beta-blockers, the angiotensin receptor blockers (ARBs) and the angiotensin converting enzyme inhibitors (ACEIs) [Whitworth & Chalmers, 2004; Alderman, 2004]. The World Health Organization International Society of Hypertension (WHO/ISH) guidelines do not exclude the use of any of these classes of anti-hypertensive medications either as first-line agents or as maintenance therapy (Whitworth & Chalmers, 2004).

The eventual choice of drugs and whether or not to start anti-hypertensive treatment with either a single agent or a combination of agents will be determined by the cardiovascular risk profile of the patient, socioeconomic considerations, the potential for end organ damage, the presence of comorbidities in the patient and other factors specific to each patient. (Pardell et al., 2000). The individualization of antihypertensive therapy is therefore an important treatment consideration to improve adherence to therapy (Lindholm, 2002) from the perspective of current practice, established treatment guidelines and recommendations in the literature (Taylor, 1990; Edmonds et al., 1990; Pardell et al., 2000; Moser, 2006; Whitworth & Chalmers, 2004).

2.5.2 Diuretics

Thiazide diuretics are a commonly prescribed class of antihypertensive drugs and these agents remove water from the body and prevent re-absorption of sodium by the kidneys (Reyes, 2002; Kaplan, 2000). The thiazide diuretics have been associated with a higher risk of developing diabetes compared to other classes of antihypertensive agents (Aksnes et al., 2006). Thiazide diuretics may therefore place certain hypertensive patients with insulin resistance at a higher risk of developing diabetes,

compared with patients who commence treatment with ACEIs or other therapies. Insulin resistance is the poor uptake and utilization of insulin for glucose metabolism by the tissues in the body (Stump, et al., 2006).

2.5.3 Beta adrenoceptor antagonists

Pharmacological blockade of the neurotransmitter receptors for norepinephrine and epinephrine lowers total peripheral resistance and cardiac output, in addition to interrupting other pathogenic mechanisms for the development of hypertension such as the renin-angiotensin system (Staffileno, 2005; Panjrath & Meserli, 2006). Beta-blockers are prescribed as monotherapy or in combination with other drugs such as diuretics in the treatment of hypertension (Prichard, et al., 2001). The beta-blockers were introduced in the early 1970s to treat hypertension and other cardiovascular disorders. Several beta-blockers are commercially available including propranolol and atenolol. Although beta-blockers reduce the cardiac output, their primary mode of action is the reduction of total peripheral vascular resistance (Ram, 2002; Staffileno, 2005).

Some of the adverse effects of beta-blockers include insomnia and depression (Ram, 2002). These agents may also affect carbohydrate metabolism negatively. They may mask insulin-mediated hypoglycemia. Beta-blockers may also cause hyperglycemia (Macleod & McLay, 1998). In susceptible individuals, beta-blockers may cause bronchospasm and considerable caution should be taken when administering beta-blockers to patients with asthma and chronic obstructive pulmonary disease (Beevers, 1998).

2.5.4 Alpha-1 adrenoceptor antagonists

The alpha adrenoceptor antagonists are used in the treatment of hypertension although, in recent times, they have not been used as widely for hypertension as they once were (Ram, 2002; Cauffield, Gums, & Curry, 1996). Available alpha-blockers include Prazosin, Terazosin and Doxazosin. The alpha-blockers may be used alone or in combination with diuretics, calcium channel antagonists or beta-blockers. The adverse effects of the alpha-blockers include headache, drowsiness and fatigue (Ram, 2002). First dose hypotension, a severe decrease in blood pressure following the first dose due to changes in the blood pressure regulation mechanisms in the body, has also been associated with Prazosin (Cauffield, et al., 1996). This phenomenon is uncommon with the second-generation alpha-blockers such as Doxazosin and Terazosin (Ram, 2002; Cauffield, et al., 1996).

2.5.5 Combined alpha and beta-blockers

Combined alpha and beta-blockers like carvedilol and labetalol block both the alpha and beta-adrenergic receptors (Ram & Kaplan, 1979). These drugs act at the beta-receptor site primarily while alpha blockade is an ancillary property. Labetalol is available to treat hypertension orally and intravenously to treat hypertensive emergencies (Ram, 2002). Carvedilol is indicated for the treatment of mild to severe heart failure. Orthostatic hypotension may occur upon the administration of large doses of combined alpha and beta-blockers. Orthostatic hypotension is a large decrease in blood pressure upon standing, which may result in fainting (Ram & Kaplan, 1979; Ram, 2002). Labetalol has been associated with the development of serious hepatotoxicity and liver failure and hence requires regular liver function tests upon administration

(Marinella, 2002). The adverse effects associated with combined alpha and beta-blockers are similar to those caused by alpha and beta-blockers as single agents (Ram, 2002; Cauffield, et al., 1996; Macleod & Mclay, 1998).

2.5.6 Central alpha adrenoceptor agonists

This class of antihypertensive agents is one of the oldest classes of antihypertensive drugs and they are still used in the management of hypertension and the metabolic syndrome (Van Zwieten, 1999; Joshi, et al., 1984). This class of drugs includes clonidine, guanabenz, guanfacine and methyldopa (Joshi, et al., 1984). The first drug in this class was methyldopa, a well tolerated and centrally acting alpha adrenoceptor agonist (Ram, 2002). The stimulation of alpha-receptors leads to a reduction in the excitatory actions of norepinephrine and epinephrine with a resultant decrease in peripheral vascular resistance and cardiac output. Methyldopa is well tolerated in pregnancy (Van Zwieten, 1999). Clonidine is the most frequently used drug in this class. The most common side effects of the centrally acting antihypertensive agents include sedation, dry mouth and reduced libido (Van Zwieten, 1999). Abrupt cessation of clonidine therapy may result in severe rebound hypertension (Ram, 2002).

2.5.7 Peripheral adrenergic inhibitors

Peripheral adrenergic inhibitors include the drugs; guanethidine and reserpine (Lederle, et al., 1993). These drugs block the sympathetic outflow from the sympathetic nervous system by depleting noradrenalin stores (Ram, 2002). Reserpine is still in use; however it is associated with adverse effects such as nasal stuffiness, peptic ulcers, diarrhea and depression (Lederle, Applegate, & Grimm, 1993; Ram, 2002). Adverse

effects associated with guanethidine include postural or orthostatic hypotension, diarrhea and drug interactions with tricyclic antidepressants (Ram, 2002).

2.5.8 Calcium channel antagonists

Calcium channel blockers are popular medications for hypertension (Curran, et al., 2006). They are effective as monotherapy or in combination with other antihypertensive drugs (Ram, 2002). This group of antihypertensive agents is commonly used in the elderly and African Americans (Ram, 2002; Curran, et al., 2006). Studies have shown a superior effect on blood pressure when calcium channel blockers are combined with diuretics. The adverse effects of the calcium channel antagonists include reflex tachycardia which can be caused by short acting calcium channel antagonists such as nifedipine (Grossman & Meserli, 2006).

2.5.9 Angiotensin receptor antagonists

The mechanism of action of the angiotensin receptor blockers is the interruption of the renin-angiotensin cascade and subsequent lowering of blood pressure (Mckelvie, 2006). Currently, a number of orally administered angiotensin receptor blockers are available for the treatment of hypertension and include losartan, irbesartan, candesartan, telmisartan, eprosartan, and valsartan. The angiotensin receptor blockers are effective alone or in combination with other classes of antihypertensive agents (See, 2001).

The pharmacological actions of the angiotensin receptor blockers are similar to that of the angiotensin converting enzyme inhibitors and include reversal of vasoconstriction, inhibition of aldosterone secretion and reversal of myocardial and vascular hypertrophy (Ram, 2002). However, unlike, angiotensin converting enzyme

inhibitors, the angiotensin receptor blockers do not interfere with bradykinin metabolism and do not normally cause the dry cough side effect associated with the angiotensin converting enzyme inhibitors (See, 2001; Ram, 2002).

2.5.10 Angiotensin converting enzyme inhibitors

The angiotensin converting enzyme inhibitors (ACEIs) are an effective, safe and well-tolerated class of anti-hypertensive agents (Ram, 2002). The ACEIs do not cause some of the adverse events associated with other classes of anti-hypertensive drugs such as the thiazide diuretics and the centrally acting anti-hypertensive agents (Wong, et al., 2004). The ACEIs are indicated for the treatment of hypertension either as monotherapy or in combination with other anti-hypertensive drugs (Wong, et al., 2004; Schoenberger, 1988; Kostis, 1988).

The ACEIs exert their anti-hypertensive action primarily, by blocking the renin-aldosterone angiotensin system [Wong, et al., 2004]. The renin angiotensin aldosterone system is a hormone system that helps to regulate blood volume and blood pressure in the body. High renin concentrations in the body triggers high blood pressure. Individuals with a high renin concentration and a hyperactive sympathetic system are likely to respond optimally to ACEIs as well as other antihypertensive agents (Ram, 2001).

The ACEIs also provide an important level of target-organ protection, which distinguishes this unique class of anti-hypertensive agents from other anti-hypertensive drug classes such as diuretics that may not provide adequate target-organ protection when compared to the ACEIs (Wong, et al., 2004). Patients with uncomplicated hypertension who are at risk of developing cardiovascular diseases or who currently have comorbid cardiovascular disease may also benefit from ACEI monotherapy

(Bicket, 2002). Despite the important clinical advantages of ACEIs, studies indicate that ACEIs are not being utilized to their full potential (Toto et al., 2004).

The ACEIs lower blood pressure by reducing total vascular resistance (Pool et al., 1988). Compared to other anti-hypertensive agents with different modes of action, the ACEIs may be the optimal first-line anti-hypertensive agent for the elderly who may have co-morbid diseases responsive to treatment with the ACEIs (Wong et al., 2003). ACEI monotherapy may reduce costs and may avoid consequent adverse events. ACEI therapy may be used in the elderly and other patient groups such as those at risk of cardiovascular disease and those with co-morbid cardiovascular disease (Chobanian et al, 2003); however, studies indicate that ACEI utilization in these populations is less than expected.

2.6 Health outcomes research

In the last two decades, there has been heightened interest in measuring the results, benefits, value and outcomes of medical care (Gerszten, 1998; Benjamin, 1995). According to the National Library of Medicine, outcomes research is aimed at assessing the quality and effectiveness of healthcare as measured by the attainment of a specified outcome such as; improved health, adherence to therapy, satisfaction with healthcare delivery, lowered morbidity or mortality, and improvement of abnormal states (Lee, et al., 2000; Weeks, 1997; Epstein, 1990; Relman, 1988).

The term “health services research” officially entered medical and pharmaceutical parlance in 1959 at a joint meeting of members of the National Institute of Health (NIH) hospital facilities research and nursing research study sections (McCarty & White, 2000). At the meeting, the name, “hospital facilities research study

section" was changed to the "health services research study section". Other researchers prefer the "outcomes research" label in reference to the field (McCarty & White, 2000; Gerszten, 1998). Although individual and institutional preferences exist as to the choice of rubric for the field, consensus exists as to the need for refinement of the methods of outcomes research and its potential to impact mainstream medical and pharmaceutical care delivery positively (Eisenberg, 1998; McCarty & White, 2000; Gerszten, 1998).

2.6.1 The evolution of health outcomes research

Stakeholders in the healthcare research enterprise such as providers and policy pundits have long been concerned about the need to quantify the value or benefits offered by healthcare delivery (Relman, 1988; Lee, et al., 2000). Early advocates for the need for the improvement of the quality of healthcare services include Ernst Codman and Florence Nightingale (McCarthy & White, 2000).

The pioneering work of Florence Nightingale from the 1840s as a leading advocate for improved medical care led to improvement in the quality of medical care in the London infirmaries and later in the Crimean War (McCarthy & White, 2000). By 1914, Ernst Codman, a surgeon called for hospitals to report the number of patients benefiting from surgery and treatment. At the time, hospitals were reporting only the number of patients treated (Lee, Earle & Weeks, 2000). Codman suggested that each hospital publish this report so that comparisons of the outcomes of care across sites may be possible (Lee, et al., 2000). The work of Codman and others such as Wade Hampton Front, an epidemiologist signaled the birth of evidence-based practices in healthcare delivery (Lee, et al., 2000).

At the turn of the twentieth century, epidemiology and public health became more established scientific fields (Weeks & Pfister, 1996). While epidemiological data related to the causes and control of infectious and non-infectious disease became increasingly prevalent, the focus of early epidemiology was not on issues of effectiveness of medical therapy. As the field of epidemiology thrived, it continued to occupy a central role in the accumulation of evidence-based health care data. (Lee, et al., 2000). The work of Cochrane, an epidemiologist led to the publication of the seminal work entitled 'Effectiveness and efficiency: random reflections on the health services', in the early 1970s (Cochrane, 1989). Cochrane chronicled the gaps evident in the National Health Service (NHS) of the United Kingdom and concluded that increased healthcare funding did not necessarily translate to improved positive results or outcomes for patients (Lee, et al., 2000; Cochrane, 1989).

In the mid 1960s, before the publication of Cochrane's book, Avedis Donabedian promoted Codman's concept of quality assessment by coining the term 'outcome' as part of his 'structure, process and outcome' model for the assessment of quality of health technology and health systems (Donabedian, 1966; Lee et al., 2000). Donabedian emerged as a central figure in the outcomes assessment 'movement' and his seminal contribution to the field advocated the use of positive treatment outcomes as the yardstick by which the success of therapy, healthcare systems and programs are evaluated (Lee, et al., 2000; Donabedian, 1981; Larson & Muller, 2002).

In the United States, the 1950s and 1960s heralded an era of rapid growth in the provision of medical services that consequently placed an economic burden on health care delivery and financing (Perrin & Valvona, 1986; Relman, 1988; Relman, 1983;

Gerszten, 1998). There was accelerated growth in hospital facilities as well as rapid advancements in science and technology (Relman, 1988; Gerszten, 1998). Additionally, the number of physicians, specialists and other healthcare providers increased within this period (Grumbach, 2002; Perrin & Valvona, 1986; Gerszten, 1998). Furthermore, the enactment of Medicare and Medicaid by 1966 meant that close to 85% of Americans had medical insurance (Oberg & Polich, 1988; Gerszten, 1998). This scenario led to increasing health care costs (Oberg & Polich, 1988; Relman, 1983; Gerszten, 1998). The key drivers of increased healthcare costs in the 1950s and 1960s appeared to be the increased number and variety of available medical services (Andersen et al, 1986; Gerszten, 1998).

By the 1970s, third party payers became increasingly concerned about the rapid growth in healthcare spending and certain changes came about as a result of this concern (Ellwood, 1988; Relman, 1988; Epstein, 1990; Lee, et al., 2000). The United States Congress passed the Health Maintenance Organization Act (HMO) Act of 1973, which was designed to curb unnecessary health resource utilization and which unfortunately did not fully achieve its set objectives (Christianson, et al., 1991). The era of increasing scrutiny of healthcare resources has continued and outcomes research has seen parallel growth, not only to identify inefficient resource utilization, but to demonstrate the value of health technologies as well (Lee, et al., 2000).

By the late 1980s and 1990s, the call for greater accountability in healthcare spending and the demonstration of objective evidence of value for money increased (Strunk, et al., 2001; Lee, et al., 2000). Paul Ellwood suggested the establishment of a massive database linking treatment and outcomes data to facilitate what he called

'outcomes management' (Ellwood, 1988). The term 'outcomes movement' was coined by Epstein in 1990, referring to the application of outcomes research methods to improve healthcare decision making, reduce healthcare-related costs and ensure the development of standards to guide physician practice (Epstein, 1990).

2.6.2 Positive and negative aspects of outcomes measurement

The movement towards outcomes assessment in healthcare presents several advantages (Eisenberg, 1998; Gerszten, 1998; Mendelson, et al., 1998). Outcomes measurement will likely stimulate greater reliance on guidelines that physicians as well as other healthcare providers can use in the selection of the most appropriate interventions (Gerszten, 1998). In addition, the application of outcomes assessment techniques will promote the identification of the most beneficial alternative in a particular setting (Mendelson, et al., 1998). Furthermore, it will monitor patient well-being, satisfaction and preferences at regular intervals in different circumstances (Eisenberg, 1998; Ellwood, 1988; Reeder, 1995).

The measurement of outcomes will increasingly ensure the availability of large amounts of clinical and outcomes data that can be used for further research aimed at improving healthcare delivery (Ellwood, 1988). Therefore, the growth of outcomes research in healthcare presents unique advantages and opportunities to improve healthcare delivery and ensure cost savings (Reeder, 1995; Mendelson, et al., 1998; Motheral & Fairman, 1997).

On the other hand, there are several barriers to the continued integration of outcomes research findings into mainstream healthcare services. For instance, there is no clear consensus as to the appropriate research methods to use when measuring

outcomes (Gerszten, 1998; Froberg & Kane, 1989). The financial cost of access to data is also another challenge associated with outcomes measurement (Gerszten, 1998). In addition, there may be challenges associated with ascertaining what constitutes appropriate care among physicians. Reviewing physician and hospital records to track variations in resource utilization may become difficult (Gerszten, 1998). Patients often seek medical care from multiple physicians and their healthcare records may be kept across multiple sites of care (Brailer, 2005). This presents challenges to the outcomes researcher seeking to gather and interpret longitudinal patient data (Brailer, 2005; Gerszten, 1998).

The successful implementation of the findings of outcomes assessment depends on cooperation between all the participants in the healthcare enterprise.. However, this cooperation may not always be present (Geigle & Jones, 1990). Some of the challenges associated with the successful integration of outcomes research findings into mainstream healthcare delivery could be methodological, financial or institutional in nature (Geigle & Jones, 1990).

2.7 The measurement of stated preferences

Preferences in health services research refer to the value attributed to a particular health state, outcome, health policy or health care intervention such as pharmaceuticals (Neumann, et al., 2000). Preferences have also been described as the value ascribed to alternative options after information on the associated risks and benefits of each alternative has been processed (Bowling & Ebrahim, 2001). Preference assessment has become an active area of outcomes research, due partly to the need to

demonstrate the value of various health interventions to third party payers (Neumann, et al., 2000).

Prior knowledge of the value or benefit attached to various health interventions may enable providers and policy makers to determine the interventions or components of health interventions that need to be provided optimally and those interventions or components of interventions that respondents require less of (Torrance, 1986; Neumann, et al., 2000; Russell et al., 2003).

Two kinds of data can be obtained from outcomes assessment: revealed preference data or stated preference data (Froberg & Kane 1989; Neumann, et al., 2000; Ryan & Gerard, 2003; Lee, et al., 2000). Revealed preference data refers to past healthcare utilization behaviour or actual market information (Mark & Swait, 2004). The advantage of revealed preference measurement is that it is based on actual decisions (Mark & Swait, 2004). The analysis and examination of retrospective databases provides a good illustration of revealed preference data (Mark & Swait, 2004).

Stated preferences are obtained from respondents where actual data does not currently exist (Champ, 2003, Brown, 2003; Thacher, 2003). Stated preferences may be obtained from patients, physicians, pharmacists and other respondents such as caregivers, using preference assessment techniques such as conjoint analysis and the discrete choice experiment (DCE) [Wellman, 2000; Neumann, et al., 2000]. Stated preference studies have the advantage of providing the researcher with the ability to simulate hypothetical scenarios and to evaluate respondent behavior under these different scenarios (Mark & Swait, 2004).

2.7.1 Preference measurement methods

The tools available to the outcomes researcher include quantitative and qualitative research techniques (Lee, et al., 2000). These research methods are useful for demonstrating value or benefit and include; the analysis of large, retrospective administrative claims datasets, meta-analysis, decision-analysis, patient satisfaction surveys and prospective clinical trials that emphasize patient-centered outcomes (Brown, 2003).

2.7.1.1 Retrospective database analysis

Retrospective database analysis utilizes revealed preference data in outcomes measurement (Mark & Swait, 2004; Motheral et al., 2003). The most commonly used sources of retrospective data are administrative medical and pharmacy claims data (Motheral et al., 2003). Other sources of retrospective data include public surveys and medical records, charts or registries. Retrospective data allows researchers to observe actual healthcare resource utilization and cost patterns as they would occur in routine clinical practice and may provide longitudinal data for longer observation periods (Berggren, 2004). The data obtained from retrospective databases usually represents a large population of people and this permits a possible evaluation of pertinent research questions in population subgroups.

2.7.1.2 Meta analysis

A meta-analysis combines the results of several studies that address a set of related study objectives or hypotheses (Fleiss & Gross, 1991; Mandelblatt et al., 2003,). Meta-analyses are performed in order to overcome the problem of reduced statistical power associated with small sample sizes of different, but related studies (Eddy et al.,

1990). A combination of several studies therefore in this case may improve statistical power of the meta-analysis study and the effect size of the meta-analysis. Meta analyses may also address questions not previously addressed by the original studies (Dickersin & Berlin, 1992; Mandelblatt et al., 2003).

In healthcare research, meta-analyses are more widely used in evidence-based medicine to demonstrate the value of treatments and other health interventions using clinical trials data. (Lee, et al., 2000). Secondary data on the efficacy, safety and other aspects of a treatment, obtained from clinical trials may be pooled across several studies to determine the value of such treatments in patients. A weakness of meta-analysis is the heavy reliance on published studies as well as the potential to include badly designed studies which may affect the conclusions of the meta-analysis (Mandelblatt et al., 2003; Cook et al., 1993).

2.7.1.3 Decision analysis

Decision analysis uses secondary data from randomized clinical trials, cost of illness studies and meta-analysis to determine the cost effectiveness of competing treatment alternatives (Mandelblatt et al., 2003). Decision analytic tree models and Markov models or state transition models are the most common tools for decision analysis in outcomes research (Weinstein, 1980).

Decision analytic tree models simulate the sequence of chance events and decisions over a relatively short period of time, unlike the Markov models which can model disease progression for relatively longer periods of time and permit transitions from one health state to another (Mandelblatt et al., 2003; Mandelblatt et al., 1992). Each chance event is assigned a probability obtained from clinical trial data and each

path through the final decision tree model represents a single sequence of chance and decision events. Each alternative treatment strategy may be evaluated by calculating the expected utility associated with that alternative (Littenberg & Sox, 1988). Cost estimates and weighted utilities are included in decision trees in order to determine the cost effectiveness of treatment alternatives (Mandelblatt et al., 2003).

Markov models are also called state transition models and they differ from decision tree models in several ways (Beck & Pauker, 1983; Weinstein et al., 1987). State transition models may be used to simulate clinical events over a patient's lifetime. Furthermore, state transition models permit the simulation of various health states such as various degrees of disability (Beck & Pauker, 1983). These models also allow for the possibility of the eventual death of the patient from disease progression. Transition probabilities determine the chance of an individual remaining or moving to another health state (Weinstein et al., 1987). Markov models can also be used to model population transition between health states and have been used to determine outcomes in cost effectiveness studies (Beck & Pauker, 1983).

2.7.1.4 Clinical trials and patient-reported outcomes

Randomized clinical trials have increasingly included patient-reported outcomes as part of the data collected from participants (McCabe & Friedman, 1992; Lee, et al., 2000). These studies have been referred to in the literature as "piggyback" studies (Torrance, et al., 2003). Typically, health-related quality of life and preference data may be collected in these studies along with healthcare resource utilization data.

These studies provide several advantages including the fact that study participants are randomized to treatment arms, are blinded to the treatments received

and the experimental conditions may be controlled. These studies therefore have high internal validity. The disadvantage of clinical trials that have an adjunct patient-reported outcome study is a low external validity or ability to generalize study findings to the general population. There could also be costs and outcomes that are specific to the clinical trial environment, which is not applicable in actual practice. This serves to reduce the external validity or representativeness of these kinds of studies (Torrance, et al., 2003).

2.7.1.5 Willingness to pay or contingent valuation surveys

Willingness to pay or contingent valuation is a stated preference measurement technique that uses survey techniques to elicit monetary estimates of the value of health states and health interventions such as pharmaceuticals (Diener, et al., 1998). Willingness to pay or contingent valuation surveys present hypothetical scenarios to respondents in order to obtain monetary preference estimates for health states or health interventions. These techniques have origins in the welfare and environmental economics literature (Brown, 2003). The contingent valuation technique is increasingly being applied to the elicitation of preference values for healthcare states and interventions (Diener, et al., 1998). The technique has been used to estimate willingness to pay for in-vitro fertilization (Neumann and Johannesson, 1994) and to estimate demand for a HIV/AIDS vaccine (Whittington et al., 2002).

2.7.1.6 Cost benefit analysis

Cost benefit analysis is an economic evaluation technique with origins in welfare economics (Liljas & Lindgren, 2001; Johannesson, 1996; Garber, et al., 2003). Cost benefit analyses are being used increasingly in health outcomes measurement to

determine the value of health programs and interventions. (Johannesson, 1996). Cost benefit analyses differ from other economic evaluation techniques such as cost effectiveness analyses, in how the outcomes are quantified. Unlike the other economic evaluation techniques, cost benefit analyses value outcomes in monetary terms (Johannesson, 1996). Because outcomes or benefits of programs are measured in monetary terms and can be compared to the costs of the programs, the decision makers' budgetary constraints may serve as the decision criterion (Garber, et al., 2003). Table 3 compares cost benefit analyses with other economic evaluation techniques.

The benefits portion for cost benefit analyses may be obtained using willingness to pay or contingent valuation surveys (Brent, 2003). Willingness to pay surveys provide a monetary value of benefit which can then be compared to the costs of the program before a decision is made regarding the feasibility of the health program or intervention (Brent, 2003).

2.7.1.7 Conjoint analysis

Conjoint analysis is a stated preference assessment technique with origins in the transport economics, environmental economics and marketing research literature (Ryan, 2004; Mark & Swait, 2004). Conjoint analysis has traditionally been used to establish what characteristics, attributes or factors influence the demand for various commodities or services. Ultimately, the results of a conjoint analysis could determine what combinations of factors could maximize the value of such products or services (Ryan, 1999). In the healthcare field, conjoint analysis is increasingly being used to determine patient preferences for healthcare interventions and technologies (Ryan, et al., 1998). The recent applications of conjoint analysis shows that the technique can be

used to value the benefits associated with the attributes or characteristics of healthcare programs (Ryan, 1999). DCEs are a subtype of conjoint analysis that measure patient preferences in terms of consumer choice (Ryan & Gerard, 2003).

2.7.1.8 Discrete choice experiments

Discrete choice experiments are a subtype of conjoint analysis based on the premise that goods and services can be described by their attributes (Ryan & Gerard, 2003; Ryan, et al., 2001; Ryan, 1999). Discrete choice experiments involve presenting respondents with sets of product scenarios described in terms of the attributes or characteristics of the products of interest (Ryan, 1999). Respondents are then asked to make a product choice based on their preferred scenario. The data obtained are modeled statistically based on whether or not the characteristics of the product of interest are important or not (Ryan, 1999). The relative importance of characteristics or attributes and the trade offs that occur between characteristics or attributes may also be obtained statistically (Ryan & Gerard, 2003; Ryan, 1999; Ryan et al., 2004).

2.7.1.8.1 Theoretical Foundation of discrete choice experiments

Discrete choice experiments are based theoretically on Lancaster's economic theory of value (Lancaster, 1966). DCEs are attribute-based measures of preference or benefit (Ryan & Gerard, 2003) and are premised on the basis of description of goods in terms of attributes and the assignment of preference based on the levels or range of values of these attributes (Ryan & Gerard, 2003). Therefore, DCEs and Lancaster's theory both share a multi-attribute approach to the assessment of value.

Table 2.1: Summary of health economic evaluation techniques

Type of Economic Analysis	Measure of Cost	Measure of Outcomes or Effectiveness	Analytical Questions	Strengths of Technique	Weaknesses of Technique
Cost effectiveness analysis (CEA)	Monetary (dollars)	Natural units of effectiveness or survival such as: Years gained, disabilities prevented, deaths prevented	What alternative produces the highest level of effectiveness for a given cost? What alternative produces a given level of effectiveness for the lowest cost?	Easy to conduct and useful for studies evaluating a small number of alternatives	It may be difficult to interprete results or compare alternatives with different measures of effectiveness Decision criterion is subjective
Cost benefit analysis (CBA)	Monetary (dollars)	Monetary (dollars)	What alternative produces the highest monetary benefit for a given cost? What alternative produces a certain level of monetary benefit for the lowest cost?	Costs of programs or health interventions can be compared directly to the monetary value of expected benefits and an objective assessment of the program can be performed	Often problematic to place a monetary value on health
Cost utility analysis (CUA)	Monetary (dollars)	Quality adjusted life years (QALYs)	What alternative produces a given level of utility at the lowest cost or the highest level of utility at a given cost?	Incorporates individual preferences for units of effectiveness	Decision criterion is subjective
Cost minimization analysis (CMA)	Monetary (dollars)	None	Based on the existing budget, is this alternative feasible?	Alternatives that are not feasible are ruled out on the basis of cost alone before viable alternatives and their resulting outcomes are considered	Because measures of effectiveness are not examined, the overall worth of the alternative is not assessed

Adapted from: Levin, H.M., McEwan, P.J. (2001). Cost effectiveness analysis. 2nd Edition. London: Sage Publications, Pages 27-28

Lancaster's theory has found application in various fields. Initially, Lancaster's theory was applied in market research (Lancaster, 1966). Its subsequent applications include the analysis of consumer demand (Lancaster, 1971) and current applications include the measurement of patient preferences through discrete choice experiments (Ryan & Gerard, 2003). Like other stated preference techniques such as willingness to pay, DCEs utilize hypothetical scenarios to measure preferences for health outcomes associated with different pharmaceutical interventions, health states, health care policies and programs. Willingness to pay is a preference measurement technique that values health states and interventions and the characteristics of these interventions in monetary terms. Wllingness to pay estimates may be generated from DCEs (Lloyd, et al., 2005). This is possible if a cost attribute is included in the design of the discrete choice experiment (Ryan & Gerard, 2003; Lloyd, et al., 2005).

DCEs may be applied in situations where process utilities and non-health outcomes are the endpoints or variables of interest (Ryan, 1999; Hundley & Ryan, 2004). They also offer the advantage of providing utility estimates and wilingness to pay estimates for each of the attributes of healthcare interventions or programs (Lloyd, et al., 2005). Compared with other stated preference methods such as the standard gamble and time trade off techniques for estimating utilities, DCEs provide information about how the different attributes that comprise a healthcare intervention or program are weighted relative to one another (Lloyd, et al., 2005; Ryan et al., 2004). DCEs may thus be used to value the attributes that most appeal to different stakeholders in the healthcare market place such as patients, non-patients, caregivers, healthcare practitioners, the general public and policymakers (Lloyd, et al., 2005). DCEs assume

that a healthcare intervention or program can be disaggregated into its components or attributes (Ryan & Gerard, 2003).

2.7.1.8.2 The use of discrete choice experiments in healthcare

The popularity of DCEs has increased in health outcomes evaluation. DCEs have become important preference assessment tools because of their strong theoretical basis, methodological exactness and high levels of reliability and validity (Ryan & Gerard 2003, Bryan & Dolan, 2004). DCEs not only identify what the preferred alternative is, they capture the reason why a particular alternative is preferred, based on its attributes (Ryan, et al., 2001). DCEs have the important advantage of being able to generate both utilities and willingness to pay estimates. Reports of the reliability and validity of DCEs have also been positive (Ryan, 2004).

The discrete choice experiment technique has been used to value the benefits associated with interventions against acute and chronic diseases such as allergic rhinitis, epilepsy, cancer and asthma (Lloyd, et al., 2005). However, a search of the literature did not yield a discrete choice experiment assessing the value of the pharmacological management of hypertension. Therefore, the current study will fill this gap identified in the hypertension preference assessment literature.

2.8 Survey Research Methods

2.8.1 In-Person Interviews

In-person surveys are administered directly by the interviewer in the physical presence of the respondent or participant (Champ, 2003). In-person surveys possess several advantages. The interviewer has a high level of control over the administration of the survey (Mitchell & Carson, 1989; Lavrakas, 1993). The interviewer is able to

select the respondent and therefore, able to target particular demographic subgroups. Furthermore, the interviewer is able to use visual aids to explain difficult concepts to respondents and this method of survey administration is suitable for complex surveys that may need to be illustrated (Champ, 2003; Shuy, 2001).

Although in-person surveys have important advantages, there are some disadvantages. In-person surveys are usually more expensive than other survey administration techniques due to the training of interviewers, the need to compensate interviewers and respondents and travel expenses for interviewers. In-person surveys are also associated with interviewer bias which is the influence that interviewers may have on the data obtained from respondents (Singer & Presser, 1989).

2.8.2 Mail surveys

Mail surveys are the most commonly used method of survey administration (Dillman, 1991; Champ, 2003; Fowler, 2002; Mangione, 1995). These kinds of surveys have several advantages. They are associated with fewer costs, they are less complicated to administer and they do not require the presence of a trained interviewer to administer the survey (Mangione, 1995). Mail surveys avoid interviewer effects and can be completed at the respondents pace (Champ, 2003; Fowler, 2002). Visual aids, explaining difficult concepts associated with the survey, can also be included in the survey mailed to respondents (Champ, 2003; Mannesto & Loomis, 1991).

Mail surveys are associated with several challenges. They usually have a low response rate (Mattsson & Li, 1994; Mehta & Sivadas, 1995). The completion of a mail survey requires that respondents possess an ability to read and comprehend the survey purpose and items, and certain segments of the population without the necessary

literary skills may be left out of the survey Champ, 2003). Furthermore, mail surveys usually take more time to complete compared to other survey methods (Mannesto & Loomis, 1991; Champ, 2003).

2.8.3 E-mail and web-based surveys

The use of e-mail and the internet as data collection tools is increasing (Schonlau, et al., 2002; Champ, 2003). Surveys may be e-mailed to respondents or the respondent may complete the survey at a website. E-mail and web surveys have important advantages which include the ability to reach a large number of people, less expense to administer and may be associated with shorter completion times (Schonlau, et al., 2002). However, e-mail and web surveys may require computer and technical support in order to format parts of the survey and may be challenging if the population of interest does not have regular access to e-mail and the internet (Mehta & Sivadas, 1995; Champ, 2003).

2.8.4 Telephone surveys

The use of the telephone as a survey tool in the United States has increased significantly within the last three decades (Birn, 2003; Lavrakas, 1993). Before the 1960s, the proportion of households with telephones in the US was too low for telephones to be used as a viable survey technique. In 1936, less than 40% of households in the US had a telephone (Massey, 1988). By the 1970s, telephone survey methods had become increasingly popular because greater than 80% of US household had a telephone (Lavrakas, 1993).

Telephone surveys present an opportunity for quality control over the data collection process (Bernard, 2000; Visser et al., 2000). This includes the sampling process, selection of participants for the survey, the interview itself and data entry with the use of computer-assisted telephone interviews (Lavrakas, 1993; Bernard, 2000). Telephone surveys may also be associated with lower levels of interviewer bias or the variance in results obtained due to individual interviewer conduct (Lavrakas, 1993).

An important advantage of telephone surveys is the speed at which data can be collected, processed and the results presented (Shuy, 2001). Compared to mail surveys which are dependent on mail delivery times and the willingness of participants to return completed surveys, telephone surveys provide an important time advantage (Dillman & Tarnai, 1988). Telephone surveys are therefore popular methods of data collection for policy makers and other consumers of data with a need to access important, time-sensitive information to aid decision making (Lavrakas, 1993).

Telephone surveys may provide an important level of efficiency and subsequent cost savings (Shuy, 2001; Bernard, 2000) compared to other survey methods such as in-person interviews which may include some traveling and associated expenses (McNabb, 2004). Dillman and Tarnai (1988) estimated that telephone survey items take up to 20% less time to complete compared to in-person interviews. Furthermore, properly conducted telephone surveys may achieve greater response rates compared to other survey methods such as mail surveys (Visser, et al., 2000, Lavrakas, 1993). Telephone surveys may also be used as a complementary mode of data collection in conjunction with other modes of data collection such as in-person or mail surveys. For

instance, telephone interviews may be used to increase the response rate for mail surveys and also obtain additional information (Lavrakas, 1993).

Telephone interviews may also be associated with certain disadvantages. The length of time for each interview is limited (McNabb, 2004; Bernard, 2000). It may become challenging to complete a telephone interview greater than 30 minutes in length especially when the respondents are elderly (Champ, 2003). Furthermore, telephone surveys can only reach individuals living in households with telephones that are willing and able to participate in a telephone survey (Bernard, 2000,). Lastly, unlike the in-person survey technique, telephone interviews may not permit the use of visual aids to illustrate concepts associated with the survey or for the interviewer to observe the respondent (Mitchell & Carson, 1989; Champ, 2003; McNabb, 2004).

In the healthcare arena, telephone surveys have been used to obtain dietary and nutrition status information (Fox, et al., 1992), and to obtain information from residents of households in the State of Georgia, United States about factors impacting the decision to purchase imported drugs (Fincham, 2005b). In epidemiology, telephone surveys have also been used increasingly for case control and cross-sectional or general surveys (Potthoff, 1994). For instance, the relationship between marital status and obesity was investigated using telephone survey techniques (Sobal, et al., 1992). The frequency of sleep apnea in an adult population was also examined using telephone surveys (Phillips, et al., 1989). The telephone survey method has therefore been used successfully in the healthcare setting (Fincham, 2005b; Potthoff, 1994; Yang & Eyeson-Annan, 2006; Olson, et al., 1992; Phillips, et al., 1989).

2.8.4.1 Computer-assisted telephone interviewing (CATI)

A computer assisted telephone interview is a telephone interview in which an interviewer operates a computer workstation that controls both the sampling process and the administration of the questionnaire (Lavrakas, 1993; Groves & Mathiowetz, 1984; Anie, et al., 1996). The computer assisted telephone interview technique presents several advantages including the ability to monitor interviewer workflow and also ensure standardization of interview procedures and therefore reduce variability or errors due to interviewer technique (Lavrakas, 1993). An important advantage of the computer assisted telephone interview technique is the ability to enter responses or data from participants simultaneously into a computer-readable format during the survey administration (Lavrakas, 1993; Groves & Mathiowetz, 1984).

2.8.4.2 Random digit dialing

Random digit dialling generates telephone numbers randomly from a frame of all possible telephone numbers in a defined sample domain (Lepkowski, 1988; Yang & Eyeson-Annan, 2006; Olson, et al., 1992). The random digit dialing technique involves the use of probability sampling techniques to obtain a pool of listed or unlisted telephone numbers from a defined sampling frame. Random digit dialing is therefore able to obtain a sample of listed and unlisted phone numbers and in the process increase the external validity or the representativeness of the telephone survey administration (Lepkowski, 1988). The computer assisted telephone interview may be used to generate the pool of telephone numbers although the pool of telephone numbers may also be generated manually as well. There are also commercial vendors

that provide lists of telephone numbers for purchase, including pools of telephone numbers for random digital dialing surveys (Lepkowski, 1988).

2.9 Statistical analysis

2.9.1 Logistic regression

Logistic regression is a statistical technique that is used to model the relationship between a binary outcome or dependent variable and several predictor or independent variables (Menard, 1995). The independent variables may have either continuous or categorical values (Wang, et al., 2006). The theoretical logistic regression model can be written as:

$$\text{Logit}(\pi) = \beta_0 + \beta_1 X1 + \beta_2 X2 + \ldots.. \beta_n Xn + \varepsilon \quad \text{(Equation 1)}$$

Where 'logit' is the natural log of the odds of success and 'π' refers to the probability of success or choice or the probability of the expected outcome, which is a value between 0 and 1 (Vittinghoff, et al., 2005). The ß's are coefficient or utility estimates for the independent variables and β_0 is the intercept term. The magnitude of the ß's indicates the level of importance of the coefficient estimates in the model (Ryan, 1999). The direction or sign of the coefficient estimates may also indicate theoretical validity. Theoretical validity occurs when concepts behave in previously hypothesized ways. The X's are the independent variables used to predict the binary dependent variable and the 'ε' is the error term (Menard, 1995; Ryan & Gerard, 2003; Schwartz, 2003).

2.9.1 Assumptions of the logistic regression model

The logistic regression model assumes that the binary outcome variable follows a binomial distribution. The values of the binary outcome are statistically independent from each other and the probability of choice is defined by the equation:

$$P(\text{choice}) = \frac{\exp(\beta_0 + \beta_1 X1 + \beta_2 X2 + \ldots.. \beta_n (Xn)}{1 + \exp(\beta_0 + \beta_1 X1 + \beta_2 X2 + \ldots.. \beta_n (Xn)} \qquad \text{(Equation 2)}$$

2.9.2 Applications of logistic regression models

Logistic regression models have found application in the health services research literature (Kozma, 2005). Fincham (2005b) examined factors affecting the decision to purchase imported medications using logistic regression analysis. Peng and colleagues (2001) used logistic regression analysis to identify important factors that may predict pain in cancer patients. The current study used random effects logistic regression to model the relationship between the independent variables and the dependent variable. Random effects models are recommended when correlated, repeated or grouped binary data is being modeled (Fincham, 2005b; Wang, et al., 2006; Hedeker & Mermelstein, 1996). The independent variables used in this study include efficacy, adverse event profile, dosage schedule and cost corresponding to the attributes or characteristics of the ACEIs as well as sociodemographic characteristics of respondents: age, ethnicity, gender, income, education and metropolitan statistical area (MSA) location or status. The dependent variable for the current study was the probability of treatment choice with the ACEIs.

2.9.3 Chi-square test

The chi square test compares the observed frequencies with the hypothesized expected frequencies for two categorical variables (Kuzma, 1992). The resultant chi-square value is then tested for statistical significance with the appropriate degree of freedom being taken into consideration.

Chi-square tests are used to determine the independence of two variables, the homogeneity of various subgroups and whether or not there is a significant difference among proportions (Kuzma, 1992; Vittinghoff, et al., 2005). The validity of the chi-square test is dependent on the available sample size and the proportions in each category. The Fisher's exact test is used in place of the chi-square test when any of the cell frequencies are less than 5 (Vittinghoff, et al., 2005).

2.9.4 Odds ratios

The odds ratio is a measure of the strength of association between two variables or groups being compared (Ott & Longnecker, 2001). The odds ratio has been described as the ratio of an event or outcome occurring divided by the complementary probability that the event or outcome does not occur (Vittinghoff, et al., 2005). Odds ratios greater than one signifies a greater likelihood or 'greater odds' of the event or outcome occurring in the group of interest. Odds ratios can then be compared across groups. The odds ratio is a fundamental component for the interpretation of the logistic regression model (Vittinghoff, et al., 2005).

2.9.5 Relative risk

The relative risk or risk ratio is a measure of the strength of association between two variables or groups being compared (Kuzma, 1992). The risk ratio is defined as the

ratio of the event or outcome in the two groups being compared. The risk ratio or relative risk is also compatible with 2x2 contingency tables, chi-square tests of significance among categorical variables and logistic regression models (Kuzma, 1992; Vittinghoff, et al., 2005).

2.10 Treatment decision-making

According to Donabedian (1966), the quality or effectiveness of health care delivery may be measured in terms of the health outcomes produced as a result of medical care or the use of health interventions such as pharmaceuticals. Two of the most commonly measured outcomes in healthcare are satisfaction and adherence (Oliveria et al., 2002; Lindholm, 2002; Alexander, et al., 2003; Rice & Matsuoka, 2004; Zyczynski & Coyne, 2000; Sica, 2003). Although similar, these two constructs have been conceptualized separately with satisfaction being a mediating variable for adherence (Chen et al., 2005).

The structure and process of health care delivery are also important determinants of health outcomes (Donabedian, 1966). The physician-patient interaction, especially the treatment selection process, has been identified as an important predictor of outcomes such as satisfaction with drug therapy as well as adherence (Lindholm, 2002; Hulka, 1979; Haynes, 1979).

The inclusion of patient preferences for pharmacological therapy is an important way to involve patients in their own care (Speedling & Rose, 1985; Bowling & Ebrahim, 2001). Advocates for the increased participation of patients in treatment decision-making point to advantages for the patient and the healthcare system (Sokol et al., 2005; Neutel & Smith, 2003). These advantages may include improved adherence to

therapy and cost savings from cardiovascular events and hospitalizations avoided (Sokol et al., 2005; Harmon, Lefante & Krousel-Wood, 2006; Lindholm, 2002, Hulka, 1979; Sica, 2003).

Recently, the structure of the physician-patient interaction has been a subject of increasing study (Charles, et al., 1997; Makoul & Clayman, 2006; Edwards & Elwyn, 2004; Thornton, et al., 2003). Charles, Gafni and Whelan (1997) identified three models of physician-patient interaction: the paternalistic model, the informed decision making model and the professional-as-agent model. Although the prevailing model may be predicted by the particular clinical situation (Makoul & Clayman, 2006; Edwards & Elwyn, 2004), various authors have reported an increasing trend towards increased participation of patients in treatment decision making for acute and chronic diseases (Charles, et al., 1997; Murray, et al., 2006; Thornton, et al., 2003).

The conceptual framework described by Szasz and Hollender (1956) identifies mutual participation in treatment decision-making between physicians and patients as an important determinant of improved patient health outcomes in chronic disease. They posited that in patients with chronic disease, the long-term experience with drug therapy can provide important information to physicians regarding the suitability of prescribed therapy. Szasz and Hollender (1956) argue that the success of the chosen therapy may be improved if the patient is knowledgeable about the disease condition as well as willing to cooperate with the physician who ultimately determines whether or not to optimally involve the patient in treatment decisions.

The ubiquitous advertising of prescription pharmaceuticals through direct-to-consumer-advertising appears to have encouraged conversations between physicians

and their patients about the treatment options available for treating acute and chronic diseases (Kincaid, 1992; Kravitz et al., 2005; Woloshin, et al., 2001; Datti & Carter, 2005). Direct-to-consumer advertising, as well as other sources of information such as the internet, has reduced the information asymmetry existing between physicians and patients (Datti & Carter, 2006). This asymmetry exists because physicians possess specialized knowledge about diseases and treatments that was not easily accessible in the past, but is now more accessible to patients due to freely available information on the internet as well as direct-to-consumer advertising (Kravitz et al., 2005; Woloshin, et al., 2001).

Harmon and colleagues (2006) called for physicians to create the right environment conducive for shared treatment decision-making. Physicians hitherto may have assumed that they knew their patients' needs without posing questions directly to the patients (Hulka, 1979; Rost, et al., 1989). Therefore, there appears to be a further need for physicians to provide information about the characteristics or attributes of treatment to patients.

Although various factors such as shortened consultation times attenuate communication between patients and physicians, Greenfield, Kaplan and Ware (1985) suggest that active patient participation in treatment decision-making improved adherence to treatment and did not unnecessarily disrupt the physician patient interaction. Other research studying increased patient participation in treatment decision making has generally reported favorable results (Schulman, 1979; Charles, et al., 1997).

A focus on drug treatment for hypertension is important because of the high cost associated with medications for high blood pressure (Strunk & Ginsburg, 2003; Dunn & Small, 2000; Mojtabai & Olfson, 2003; Pardell et al., 2000). Up to $12 billion is spent annually on prescriptions for antihypertensive medications (Neutel & Smith, 2003; Dunn & Small, 2000; Mojtabai & Olfson, 2003). Despite the wide availability of numerous treatments for hypertension, less than 35% of patients with hypertension who are taking medications have their blood pressure well controlled (Zyczynski & Coyne, 2000; Elliot, 2003; Cushman, 2003).

Treatment-related factors affecting adherence to medications include efficacy of the medication, side effect profile of the medication, dosage convenience and cost of therapy (Lindholm, 2002; Ogedegbe, et al., 2004; Dusing et al., 1998; Alexander et al.,, 2003; Gascon et al., 2003; Salman et al., 1999; Neutel & Smith, 2003; Zyczynski & Coyne, 2000; Alexander, 2006).

Not all patients are willing to participate in treatment decision-making and would rather leave treatment decision making to physicians (Strull, et al., 1984; Arora & McHorney, 2000). In addition, the preferences of physicians and their patients for the attributes of pharmacological treatment may not always be the same (Wellman, 2000; Bowling & Ebrahim, 2001). On the other hand, there are patients who would like to participate in treatment decision-making and discuss the attributes of alternative treatments with their physicians (Bowling & Ebrahim, 2001; Oliveira et al, 2002; Ogedegbe, et al., 2004). The inclusion of the preferences of these patients in treatment decisions may improve adherence rates, avoid hospitalizations and in the process

produce cost savings (Sokol et al., 2005; Pauker & McNeil, 1981; DiMatteo & Hays, 1980).

2.10.1 Treatment decision making in hypertension

The individualization of antihypertensive therapy which considers the patients' sociodemographic and physiological status in treatment decision making is also related to the consideration of patient-related and treatment-related factors in antihypertensive treatment decision making (Bowling & Ebrahim, 2001). The elicitation of patient preferences and the consideration of factors specific to hypertensive patients in treatment decision making may improve treatment outcomes in the patient (Bowling & Ebrahim, 2001; Littenberg & Sox, 1988).

Stated preferences have been obtained previously in the hypertension outcomes research literature. Johannesson, Jonsson and Borgquist (1991) estimated direct willingness to pay using open-ended and dichotomous choice survey methods. Their findings indicated that compared to the open ended method, the dichotomous choice method provided more reliable monetary estimates of preference of Swedish patients for antihypertensive therapy. Another Swedish study by Johannesson and colleagues (1991) compared non-pharmacological treatment of hypertension with drug therapy in a cost benefit analysis framework. Non-pharmacological treatment of hypertension was associated with higher costs compared to the benefits which were estimated using willingness to pay. The drug treatment of hypertension was associated with greater benefits and did not produce a net loss (Johannesson, et al., 1991). Ramsey and colleagues (1997) estimated willingness to pay for antihypertensive therapy among members of a staff model HMO and obtained similar results as Johannesson and

others. These studies establish the possibility that preference data and willingness to pay information may be obtained successfully from hypertensive patients (Ramsey, et al., 1997). The current study used a discrete choice experiment to obtain the stated preferences of patients with hypertension for the attributes of a specific class of antihypertensive agents (the angiotensin converting enzyme inhibitors); the trade offs that patient's make among these attributes as well as willingness to pay for improvement in the levels of the attributes of the ACEIs.

The profile of the ACEIs was selected for this study for several reasons. The ACEIs are currently among the most widely prescribed antihypertensive medications in the US compared to the older drug classes such as the diuretics (Johnson & Singh, 2005; Kaplan, 1999; Toto et al., 2004; Pool, et al., 1988; Wong, et al., 2004; Kostis, 1988). The ACEIs are effective as monotherapy in up to 70% of patients with stage one hypertension (Ram, 2002; Wong, et al, 2004). Lastly, the ACEIs are able to protect the heart and kidneys which may be damaged in chronic hypertension (Ram, 2002).

2.11 Rationale and significance of the study

The factors predicting adherence to medication in hypertension and chronic disease are numerous. These factors include antihypertensive treatment attributes or characteristics such as efficacy, adverse events, out-of-pocket cost and dosage schedule. Although pharmacological treatment attributes impacting adherence in patients with hypertension have been identified, the impact of these treatment attributes on patient choice are less well investigated. An examination of the nature of patient preferences for antihypertensive therapy may further provide knowledge for physicians regarding the attributes of importance to patients and may enable physicians and other

decision makers to provide more of attributes that patients prefer. This would improve patient health outcomes such as adherence and satisfaction. This study identified the nature of patient preferences for antihypertensive therapy including the relative importance of treatment attributes and trade-offs for the attributes of the angiotensin converting enzyme inhibitors using a discrete choice experiment in a cost benefit analysis framework.

CHAPTER THREE

RESEARCH HYPOTHESES

3.0 Introduction

The review of the literature suggests that the attributes of antihypertensive and other therapy such as the efficacy (Sherer et al., 2005; Watson et al., 2004; Alexander, 2006; Lloyd, et al, 2005), adverse event profile (Ashcroft, et al.2006; Alexander, 2006; Ratcliffe, et al., 2004), dosage schedule (Sherer et al., 2005; Alexander, 2006; Beusterien et al., 2005) and cost of therapy (Phillips, et al., 2002; Ryan & Hughes, 1997; Ryan, 1999; Alexander, 2006) may impact preferences for treatment.

Although the hypertension preference assessment literature suggests that the efficacy, adverse event profile, dosage schedule and cost of therapy attributes of antihypertensive therapy may be related to patient preferences for treatment (Alexander, 2006), the relative importance of these attributes for patients as measured by a discrete choice experiment in the context of patient choice is yet to be investigated. Furthermore, the nature of patient preferences for these attributes considering a specific class of antihypertensive agents such as the ACEIs is also unknown. It is important to study the relative importance ascribed to treatment attributes in order to improve adherence and enhance other treatment outcomes.

The review of the literature is also indicative of the varying nature of the relationships between sociodemographic variables such as age (Say et al, 2006; Degner & Sloan, et al., 1992; Stiggelbout & Kiebert, 1997; McKinstry, 2000; Duric &

Stockler, 2001), gender (Degner & Sloan, 1992; Arora & McHorney, 2000; Yellen & Cella, 1995), income (McKinstry, 2000; Bruera, et al., 2002; Wright, et al., 1994), education (Thompson, et al., 1993; McKinstry, 2000; Bruera, et al., 2002) and geographical location (Anell, et al., 1997) and patient preferences for treatment. The nature of the relationship between sociodemographic variables such as age, gender, income, education and patient preferences for therapy may be context-specific and dependent on the way in which the studies were completed.

The research hypotheses are presented in the context of the ACEIs. All tests of significance were performed at the 5% level of confidence (Hatcher & Stepanski, 1994). The binary or dichotomous outcome variable of this study calls for the application of logistic regression modeling.

3.2 Research hypotheses

Objective 1: What is the relative importance of the perceived efficacy, adverse events, cost of therapy and dosage schedule attributes of antihypertensive treatment in adult patients?

Objective 2: What are the effects of patient preferences for varying treatment attributes, trade-offs among treatment attributes and patient demographic characteristics (age, gender, ethnicity, education, income and MSA location) upon patient choice to purchase a prescription for an ACE Inhibitor?

Ho_1 Perceived efficacy of treatment has no effect on patient choice of treatment with the ACEIs.

Ho_2 Risk of adverse events has no effect on patient choice of treatment with the ACEIs.

Ho_3 Dosage schedule has no effect on patient choice of treatment with the ACEIs.

Ho_4 Cost of therapy has no effect on patient choice of treatment with the ACEIs.

Ho_5 Age has no effect on choice to purchase antihypertensive therapy with the ACEIs; there is no difference in choice to purchase antihypertensive therapy between patients younger than 65 years of age and patients 65 years of age and older

Ho_6 Gender has no effect on choice to purchase antihypertensive therapy with the ACEIs.

Ho_7 Household income has no effect on choice to purchase antihypertensive therapy with the ACEIs.

Ho_8 Education has no effect on choice to purchase antihypertensive therapy with the ACEIs; there is no difference in choice to purchase antihypertensive therapy between patients with less than a college education and patients who have some or more college education.

Ho_9 MSA location has no effect on choice to purchase antihypertensive therapy with the ACEIs.

The treatment attributes correspond to the efficacy, adverse events, dosage schedule and cost profile of the ACEIs. The impact of these attributes on patient choice for ACEI therapy forms the basis of the hypotheses. In addition, the impact of patient sociodemographic factors on patient preferences for ACEI therapy was examined as well.

CHAPTER FOUR

RESEARCH DESIGN AND METHODS

4.1 Overview

The effect of the attributes of antihypertensive therapy, particularly the effects and relative importance of the characteristics of the ACEIs such as efficacy, adverse event profile, dosage schedule and cost of therapy attributes as well as patient sociodemographic characteristics on patient treatment choice was determined. Subsequently, the trade offs that patients make among the attributes of ACEI treatment was assessed through a marginal rate of substitution (MRS) analysis. A DCE was employed to address the objectives of this study. A sample of hypothetical adult hypertensive patients was obtained through the Georgia poll, a random-digit dialled telephone survey administered through the Survey Research Center (SRC) of the Institute for Behavioral Research of the University of Georgia.

4.2 Telephone survey method

The telephone survey method was chosen over other survey methods for this study due to several advantages associated with telephone surveys. Telephone surveys present the opportunity for quality control over the data collection process (Bernard, 2000; Visser, et al., 2000). Telephone surveys are also associated with lower levels of interviewer bias or the variance in results obtained due to individual interviewer conduct (Lavrakas, 1993). Data can be obtained relatively quickly with telephone surveys compared to other sampling methods such as mail surveys that depend on time of

return of completed surveys by respondents. In addition, telephone surveys provide an important level of efficiency and subsequent cost savings (Bernard, 2000) compared to other survey methods such as in-person interviews that may include some traveling and associated expenses (McNabb, 2004). Finally, properly conducted telephone surveys may achieve greater response rates compared to other survey methods such as mail surveys (Visser, et al., 2000; Lavrakas, 1993).

4.2.1 Random digit dialling

Random digit dialling is a telephone sampling methodology that generates telephone numbers randomly from a frame of all possible telephone numbers in a defined sample domain (Lepkowski, 1988). The Georgia poll generates telephone numbers through stratified sampling ensuring that a probability sample is extracted from all possible telephone numbers in the State of Georgia, US. The study design called for the completion of 500 telephone interviews from a random digit dialing sample of households in Georgia (SRC, 2005). Adult residents of households in the State of Georgia U.S with telephones constituted the sampling frame for this study. These Georgia residents had an equal or nearly equal probability of being selected as participants for this study (SRC, 2005).

4.3 Survey administration

Each respondent was presented with the 16 randomized profiles (items) through the computer adaptive telephone interviewing system of the Survey Research Center of the University of Georgia. Each respondent was then asked through a telephone questionnaire whether or not they would take a prescription drug for hypertension corresponding to each of the 16 profiles of the ACEIs. Prior to obtaining data from

respondents, approval for the study was obtained from the Institutional Review Board (IRB) of the University of Georgia. Trained interviewers and their supervisors were responsible for administration of the survey and ensuring that data of high quality was obtained from respondents. The appendix presents the 16 profiles or items read to respondents over the telephone.

4.4 Data source and sampling frame: the Georgia Poll

The Georgia poll is a random digit dial telephone survey of adults 18 years or older in the State of Georgia, U.S. The resulting data from the survey administration included a vector of demographic variables: gender, education, income, age and MSA/non-MSA status.

4.5 Logistic regression

The current study used random effects logistic regression. Random effects logistic regression models are recommended when correlated, repeated or grouped binary data is modeled (Fincham, 2005b; Wang, et al., 2006; Hedeker & Mermelstein, 1996). Equation 1 below presents the full logistic regression equation for this study.

$$\text{Logit}(\pi) = \beta_0 + \beta_1(\text{efficacy}=X1) + \beta_2(\text{adverse events profile}=X2) + \beta_3(\text{cost}=X3) + \beta_4(\text{dosage schedule}=X4) + \beta_5(\text{age}=X5) + \beta_6(\text{gender}=X6) + \beta_7(\text{education}=X7) + \beta_8(\text{income}=X8) + \beta_9(\text{MSA location}=X9). \quad \text{(Equation 1)}$$

Where 'logit' is the natural log of the odds of success and 'π' refers to the probability of success or choice or the probability of the expected outcome which is a value between 0 and 1. The ßs are coefficient or utility estimates for the independent variables and β_0 is the intercept term. A statistically significant independent variable

indicated importance of that variable in the determination of treatment choice. The magnitude of the ßs indicates the level of importance of the coefficient estimates in the model (Ryan, 1999). The relationship between the probability of choice and a continuous predictor variable (x) was approximated by the logistic regression model as shown in Figure 4.1 (Vittinghoff, et al., 2004).

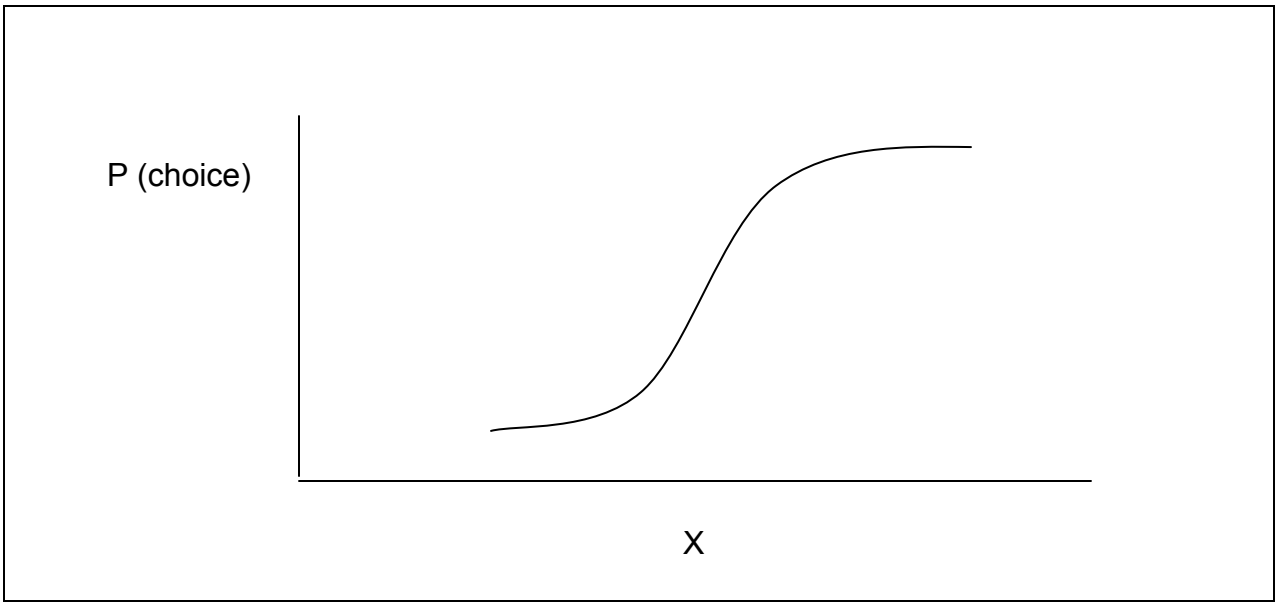


Figure 4.1: Logistic regression model

The Logistic regression model for a vector of predictor or independent variables is defined by equation 2 which permits the calculation of the probability of choice of therapy with the ACEIs for respondents.

$$\text{Probability (choice)} = \frac{\exp(\beta_0 + \beta_1 X1 + \beta_2 X2 \ldots \beta_9 X9)}{1 + \exp(\beta_0 + \beta_1 X1 + \beta_2 X2 \ldots \beta_9 X9)} \qquad \text{(Equation 2)}$$

The logistic regression coefficients are interpreted as the effect of a one unit increase in the independent variable on the outcome or dependent variable while

holding other independent variables constant. The statistical significance, magnitude and direction of the independent variables in determining treatment choice with the ACEIs at the 5% level of significance were tested using the logistic regression model.

Odds ratios may be computed by calculating the exponentials of the logistic regression coefficients and are interpreted in terms of the likelihood of the outcome event (treatment choice with the ACEIs) occurring. Odds ratios less than 1 indicate a decreased likelihood of the outcome event occurring while odds ratios greater than 1 indicate an increased likelihood of the outcome event occurring (Vittinghoff, et al., 2004). Odds ratios and other statistics were obtained using the STATA software. (StataCorp 2005, Stata Statistical Software: Release 9.0, College Station, TX)

4.5.1 Assessment of model fit

According to Hosmer and Lemeshow (1989), the assessment of model fit should subsequently follow the fitting of the logistic regression model. The STATA output provides the values for the likelihood of each model and can also be used to perform the likelihood ratio tests (Hosmer & Lemeshow, 1989; Vittinghoff, et al., 2004).

An initial logistic regression model with estimates of the effects of the attributes of the ACEIs (efficacy, adverse event profile, dosage schedule and cost of therapy) as well as the sociodemographic variables was fitted [full model]. Two models [nested models] estimating the effect of the treatment attributes of the ACEIs on the probability of treatment choice and the effect of the sociodemographic variables on the probability of treatment choice was estimated and the proportion of variance explained by these models was obtained. The likelihood ratios of the full model and the nested models

were subsequently obtained by calculating the equation below which yields the likelihood ratio statistic (Hosmer & Lemeshow, 1989)

- 2 L (nested model) – L (full model) (Equation 3)

The likelihood ratio tests are useful to assess the effects of groups of predictors on the dependent variable. A statistically significant value obtained from equation 3 indicates that collectively, the variables in a nested model make a contribution to the logistic regression model. The Pseudo R2 statistic which also indicates model fit was also examined with a higher, significant pseudo R2 indicating better model fit. The STATA output provides all of these estimates as well.

4.6 Operational definitions and variables

4.6.1 Independent variables

This study assessed the effects of treatment-related attributes and sociodemographic characteristics on the dependent variable of interest for this study, patient treatment choice. The treatment-related variables included efficacy, adverse events profile, dosage schedule and cost of therapy associated with the ACEIs. The sociodemographic variables included age, gender, income, education, ethnicity and geographical location (MSA/non-MSA geographical location).

4.6.1.1 Treatment-related attributes

DCEs are founded on the premise that a product or service can be described in terms of its attributes or characteristics (Ryan, et al., 2001; Lancaster, 1966). The procedure outlined by Ryan (1999) for the design and conduct of conjoint analyses and DCEs was followed in this study. The first step involved the determination or selection of the attributes of the intervention under consideration and the assignment of levels to

these attributes. For the ACEIs, these are the attributes that may impact patient preferences or treatment choice. The four attributes selected for this study included the efficacy of the ACEIs, the adverse event profile of the ACEIs, the dosage schedule of the ACEIs and the cost of therapy associated with the ACEIs. The 4 attributes selected were less than 9, the maximum number of attributes or characteristics suggested by Miller (1956) and Froberg & Kane (1989) for information processing.

The treatment-related attributes and their corresponding levels for this study were determined by a review of the clinical literature on the ACEIs (Vuong & Annis, 2003; Laverman, et al, 2002; Warner & Perry, 2002; Bicket, 2002). Information posted on the web pages of the following organizations was also reviewed in order to assign levels to the cost of Regents of the University System of Georgia, 2007), ExpressScripts (ExpressScripts, 2006), *Consumer Reports* (Consumer Reports Best Buy Drugs, n.d), the Centers for Medicare and Medicaid Services (CMS, n.d) and Aetna Medicare (Aetna Medicare, 2007). The information describing the attributes of the ACEIs was included in an introductory preface (Table 4.1). Table 4.2 presents the selected attributes and levels of the ACEIs.

4.6.1.1.1 Efficacy

Efficacy was defined in terms of the ability of the ACEIs to reduce blood pressure to normal levels and the ability of the ACEIs to provide target organ protection for the heart and kidneys (Vuong & Annis, 2003). Two levels were assigned to the efficacy attribute reflecting a slightly higher than normal or a slightly lower than normal chance of experiencing efficacious therapy with the ACEIs.

4.6.1.1.2 Adverse event profile

The adverse event profile of the ACEIs was defined in terms of the likelihood of the following general adverse events occurring: dry cough, dizziness, headache, dizziness and fatigue or tiredness associated with taking the ACEIs. These are some of the most commonly reported side effects associated with the ACEIs (Warner & Perry, 2002). Two levels were assigned to the adverse event attribute reflecting a high or a low risk of experiencing these adverse events.

4.6.1.1.3 Dosage schedule

The dosage schedule was defined in terms of the number of times a day that the ACEIs would be taken. Two levels were defined for this attribute: once a day and three times a day, representing the range of recommended daily dosage associated with the ACEIs (Bicket, 2002).

4.6.1.1.4 Cost of therapy

The cost of therapy was determined in terms of the possible co-payments for individuals younger and older than 65 years in health plans in the State of Georgia, U.S. The literature on the cost of ACEI therapy, based on co-payment levels was also reviewed (Huskamp et al., 2003). Co-payment information was obtained from the web pages of the following organizations: the Board of Regents of the University System of Georgia (Board of Regents of the University System of Georgia, 2007), ExpressScripts (ExpressScripts, 2006), *Consumer Reports* (Consumer Reports Best Buy Drugs, n.d), the Centers for Medicare and Medicaid Services (CMS, n.d) and Aetna Medicare (Aetna Medicare, 2007). The 16 profiles or items to be presented to respondents are presented in the appendix.

Table 4.1: Introductory preface

The following questions are about the characteristics of a type of prescription drug for high blood pressure. Having high blood pressure over a long period of time can cause serious complications which can damage organs such as the heart and the kidneys.

If you do not have high blood pressure, please assume that you do, in order to answer these questions. Assume also that you will be paying a portion of the cost for the drug out of your own pocket. Lastly, assume that you have the alternative of asking your doctor for another drug for high blood pressure.

Efficacy refers to the ability of the drug to reduce high blood pressure to normal levels and to protect the heart and the kidneys from the complications of high blood pressure such as heart failure and kidney failure respectively. Heart failure occurs when the heart looses its ability to pump blood efficiently. Kidney failure occurs when the kidneys loose their ability to concentrate urine and remove waste material from the body.

General side effects of the drug refer to the risk of having headache, dizziness, fatigue and dry cough that may occur as a result of taking the drug. The cost is the amount of money you will pay out-of-pocket for the drug every month. This amount may be as small as $10 or as high as $40. The dosage is the number of times a day that you will need to take the drug.

I will now read a set of scenarios to you and for each one, please tell me whether or not you would take the drug based on the efficacy, general side effects, cost of the drug and dosage.

Thank you for listening to this information.

Table 4.2: Attributes and levels selected for the ACEIs

Attributes	Levels
1. Efficacy of the drug	Slightly lower chance of reducing high blood pressure and protecting the heart and the
	Slightly higher chance of reducing high blood pressure and protecting the heart and the
2. General side effects of the drug	Low risk of general side effects of the drug
	High risk of general side effects of the drug
3. Cost	$ 10 / month
	$ 40 / month
4. Dosage	Once a day
	Three times a day

Table 4.3: Randomized profiles (items) for the DCE telephone survey

Question	Chance of lowering blood pressure and protecting the heart and kidneys	Risk of experiencing general side effects of the drug	Cost	Dosage	Would you take the prescribed drug – Yes or No?
1	Slightly lower	Lower	$40	Three times a day	
2	Slightly lower	Higher	$10	Once a day	
3	Slightly lower	Higher	$40	Once a day	
4	Slightly higher	Higher	$40	Three times a day	
5	Slightly lower	Higher	$40	Three times a day	
6	Slightly lower	Lower	$40	Once a day	
7	Slightly higher	Higher	$10	Once a day	
8	Slightly higher	Higher	$40	Once a day	
9	Slightly higher	Lower	$40	Once a day	
10	Slightly higher	Lower	$10	Once a day	
11	Slightly higher	Higher	$10	Three times a day	
12	Slightly lower	Lower	$10	Three times a day	
13	Slightly higher	Lower	$10	Three times a day	
14	Slightly lower	Higher	$10	Three times a day	
15	Slightly lower	Lower	$10	Once a day	
16	Slightly higher	Lower	$40	Three times a day	

4.6.1.2 Sociodemographic variables

The sociodemographic variables associated with this study included age, gender, ethnicity, income, education and MSA status. These sociodemographic variables are standard variables obtained on the twice yearly administrations of the Georgia Poll (Survey Research Center, 2005). The sociodemographic variables and categories or levels are described in Table 4.4.

Table 4.4: Sociodemographic variables

Sociodemographic variable	Levels
1. Gender	Male, Female
2. Ethnicity	White, African-American, Asian/Pacific Islander, Multi-racial /Other Hispanic
3. Age	18 or older
4. Education	< High school High school grad/GED Some college College grad or higher
5. Income	<$15,000 $15,000 - $34,999 $35,000 - $49,999 $50,000 - $74,999 $75,000 or more
6. MSA/non-MSA	MSA Location Non-MSA Location

Source: Survey Research Center, 2005

For the data analysis, the efficacy, adverse event and dosage schedule variables of the ACEIs were discrete in nature. The levels of the discrete variables were dummy coded (0 and 1). The cost of therapy variable had categorical values with levels of $10 and $40. The gender, income, ethnicity, education and MSA status variables had categorical values. For the age variable, continuous values were obtained from the respondents and used for the data analysis.

4.6.2 Dependent variables

The dependent or outcome variable for this study, patient treatment choice, was a measure of patient preferences (Ryan, 1999). Patient treatment choice can be measured directly as a dichotomous or binary variable using the DCE framework. It is possible to use a binary variable to represent patient treatment choice in a DCE framework because DCEs model the likelihood of whether or not a respondent makes a product or treatment choice. If the respondent chooses a product or treatment based on its profile, the response corresponds to a 'yes'. However, if the respondent does not choose the product or treatment, the response corresponds to a 'no'. The 'yes' and 'no' responses may then be dummy coded (1 and 0) for the data analysis. Logistic regression modeling is used to analyze data from the DCE because logistic regression can be used to model binary outcome data incorporating either discrete or continuous independent variables.

4.6.2.1 Patient treatment choice

Patient treatment choice is a dichotomous or binary variable having the values 'Yes' or 'No'. Each respondent provided either a 'yes' or a 'no' answer to each of the 16 questions representing the 16 profiles of the ACEIs generated with the Statistical

Analytical Software [SAS®] software (SAS Institute Inc, Version 9.1, Cary, NC) and subsequently randomized manually.

4.6.2.2 Willingness to pay

Willingness to pay was derived indirectly from a DCE through an MRS or trade off analysis. The trade offs among the attributes of the ACEIs refer to the degree at which respondents were willing to give up one unit of an attribute for an increase in another attribute (Ryan et al., 2001; Ryan, 1999). Willingness to pay for improved efficacy was obtained by finding the ratio of the coefficient estimate for efficacy and the coefficient for the cost variable. Similarly, willingness to pay for lower occurrence of general adverse events and once daily administration of ACEI treatment was obtained by finding the ratio of the coefficient estimates of these variables and the cost variable. Although a willingness to pay analysis is not a direct objective of this study, it is another measure of patient preference.

4.7 Profile selection, randomization and administration

The attributes and levels chosen resulted in 16 possible profiles or scenarios comprising different levels of efficacy, adverse event, dosage schedule and cost of therapy associated with the ACEIs (2 x 2 x 2 x 2 = 16). The 4 treatment attributes, each having two levels were chosen, taking into consideration that if a larger number of attributes and levels had been selected, the potential for respondent burden over the telephone would have been high. The 16 profiles were generated with the Statistical Analytical Software [SAS] (SAS, Version 9.1, Cary, NC). These profiles corresponded to a full factorial DCE design.

A full factorial DCE design uses all of the attributes and levels generated in the profile design phase. Full factorial designs are associated with the following advantages. First of all, full factorial DCE designs maximize the properties of balance and orthogonality among attributes. A balanced DCE design has all the levels of the attributes appearing an equal number of times in the total number of available profiles. An orthogonal DCE design minimizes multicollinearity among profiles (Ryan, 1999; Ryan & Gerard, 2003). Full factorial designs are thus efficient designs. Furthermore, full factorial designs allow for the estimation of interaction effects among attributes if desired (Ryan & Gerard, 2003). On the other hand, large full factorial designs include large numbers of profiles or items which may be impractical for respondents to evaluate. Therefore, full factorial designs are more practical if the numbers of attributes and levels to be evaluated are not large (Ryan & Gerard, 2003).

The next step in the design of a DCE involves the determination of which profiles to present to respondents. For this study, all of the 16 profiles or items were presented to each respondent (full factorial). The 16 profiles were selected by SAS software in order to maximize the property of level balance and to minimize multicollinearity among the profiles. Table 4.3 presents a grid of the full factorial randomized profile or items presented to respondents over the telephone.

The subsequent stage in the conduct of DCEs involved the determination of preferences for profiles presented to respondents (Ryan, 1999; Ryan & Gerard, 2003). This study used patient treatment choice as the determinant of preference for treatment with the ACEIs. Compared to ranking or ratings-based items, discrete choice items

presented to patients may mimic real-life scenarios better since individuals may be more familiar with making product choices or actual purchase decisions (Ryan, 1999).

4.8 Data analytic techniques

The data from this study was analyzed using logistic regression to model the effect of the ACEI treatment attributes and the sociodemographic variables on patient treatment choice, a dichotomous variable. The significance or otherwise of the independent variables as predictors of patient choice was determined using STATA software. Coefficients obtained from the logistic regression models were used to conduct a marginal rate of substitution analysis. The ratio of any two coefficients produces the marginal rate of substitution between the two attributes generating the coefficients. This information indicates the rate at which an individual will trade between attributes (Ryan, 1999).

4.9 Statistical software

The SAS software was used to generate the 16 profiles of the ACEI that was presented to respondents. STATA (StataCorp 2005, Stata Statistical Software: Release 9.0, College Station, TX) software was also used to perform the random effects logistic regression analysis of the data in order to examine the relationship between the independent variables and patient treatment choice with the ACEIs. The data was converted from SPSS (SPSS Inc, Chicago, IL) format to Microsoft Excel (Copyright 2007 Microsoft Corporation, Redmond, WA) format using the STATA transfer program (Stat/Transfer File Utility for Windows, Circle Systems, Seattle, WA).

4.10 Summary

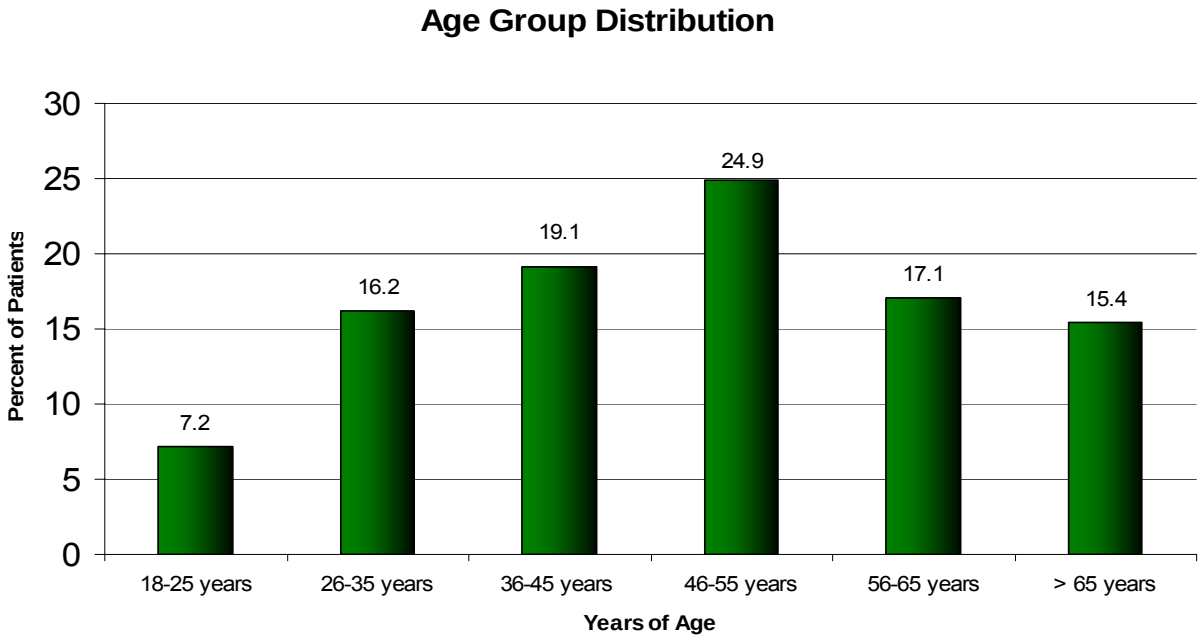
This study employed a DCE and random-digit dial telephone survey to evaluate patient preferences for ACEI antihypertensive therapy among a randomly selected sample of adults, 18 years or older in the State of Georgia, U.S. Using cross-sectional data, the impact and relative importance of the treatment attributes of the ACEIs as well as the impact of sociodemographic variables on patient choice was examined.

CHAPTER 5

RESULTS

5.1 Descriptive Statistics

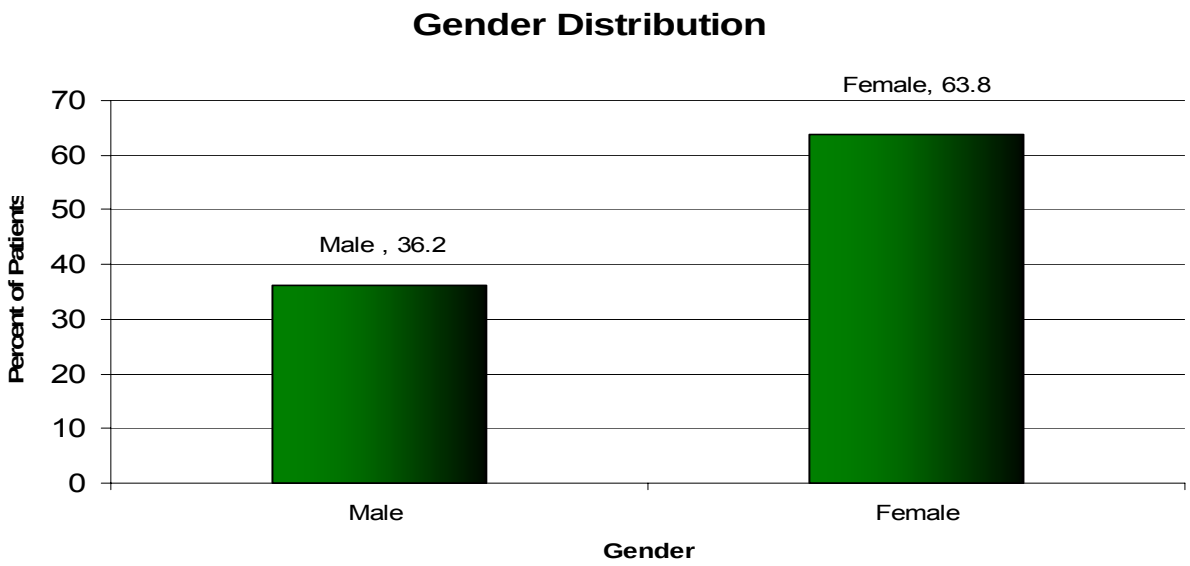
Data was collected for this study through the Survey Research Center of the University of Georgia. A total of 538 responses were obtained from the telephone survey conducted in the fall of 2006, using adults, 18 years and older residing in the State of Georgia. A majority of the respondents were female (63.8%) and Caucasian (73.9%). Slightly over half of the respondents (55.02%) had attained some level of college education or less and a majority of respondents (31.6%) had annual household incomes between $35,999 and $49,999. About a third of the sample of respondents had annual household incomes greater than $75,000. The mean age of the sample was 48.5 years (s.d. = 15.7) and 82.9% of the sample was younger than 65 years. In addition, 78.3% of the population resided in metropolitan areas, which are contiguous areas of high population density. The sample was fairly representative of the adult population of the State of Georgia. Figures 5.1 to 5.6 summarize the descriptive characteristics of the respondent sample.



N = 538

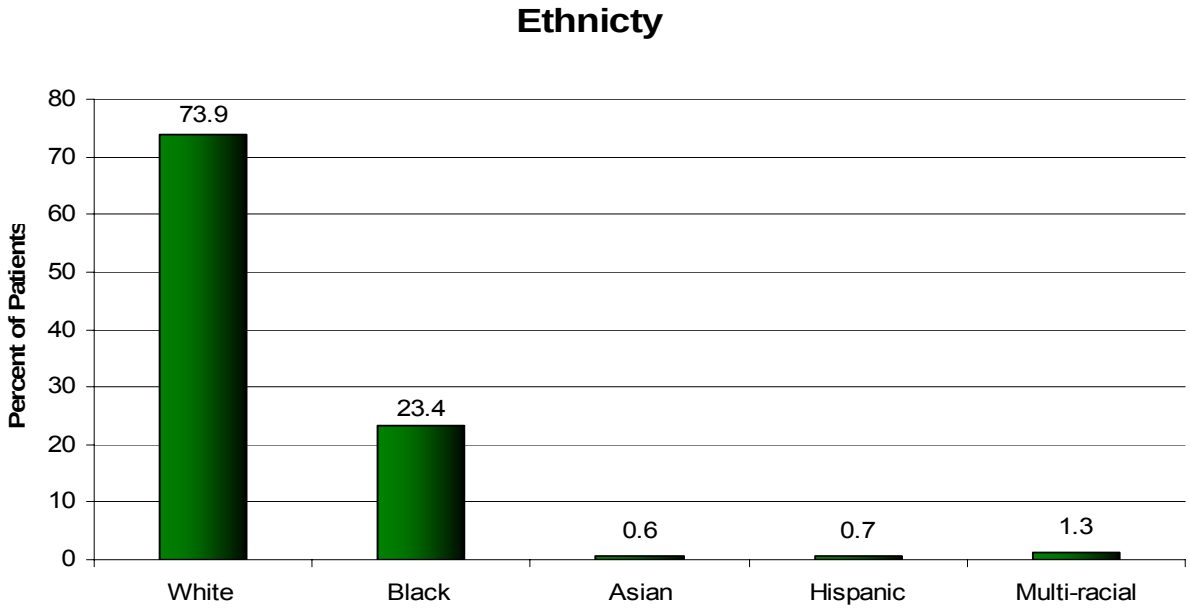
Figure 5.1: Age group distribution

The majority of respondents (24.9%) belonged to the 46-55 year age group. The respondent population consisted of both individuals who currently have hypertension as well as those who are normotensive. Although the 46-55 year age group and older age categories may consist of a higher proportion of individuals who are currently hypertensive, compared to younger respondents, the elicitation of patient preferences for the treatment of hypertension from younger respondents represents a valid approach in the preference assessment literature. According to Gold and colleagues (1996), patient preferences for treatment should be obtained from two types of respondents; patients with the disease in question and individuals who are likely to develop the disease in future. Therefore, it is important to elicit patient preferences from respondents of different age categories, based on recommendations in the literature.



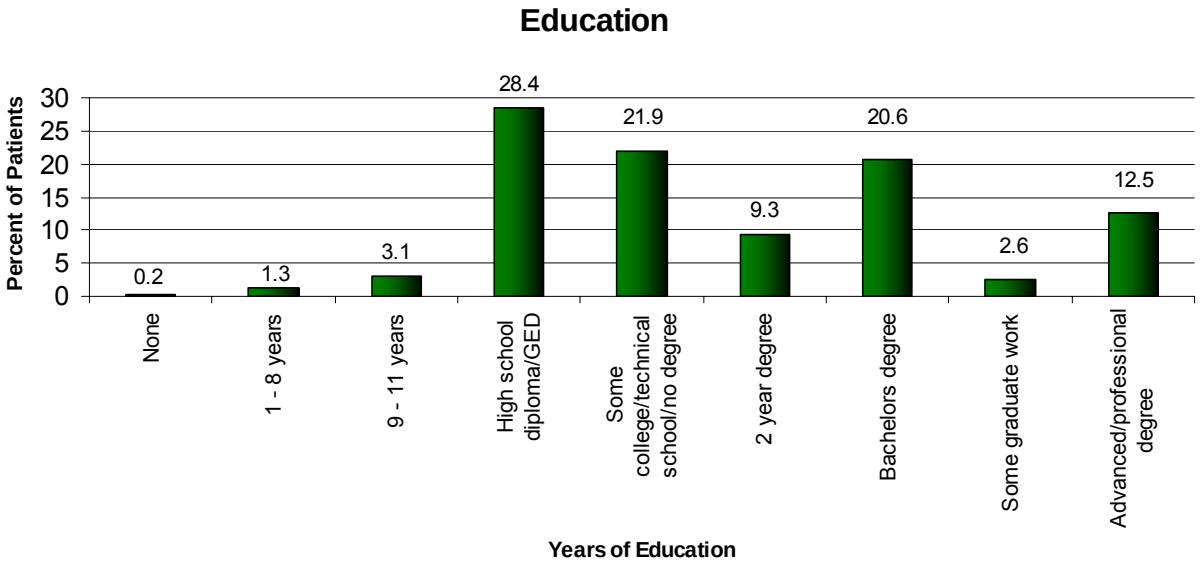
N = 538

Figure 5.2: Gender distribution



N = 538

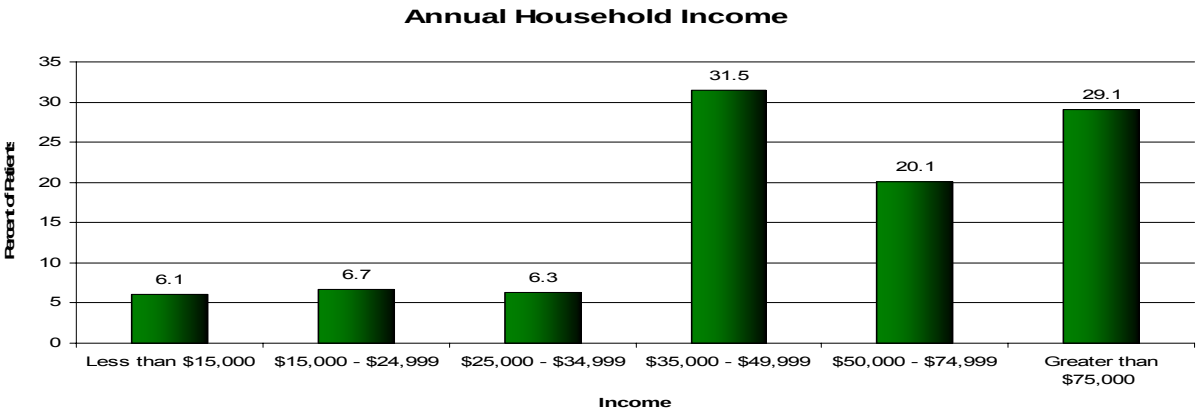
Figure 5.3: Ethnicity distribution



N = 538

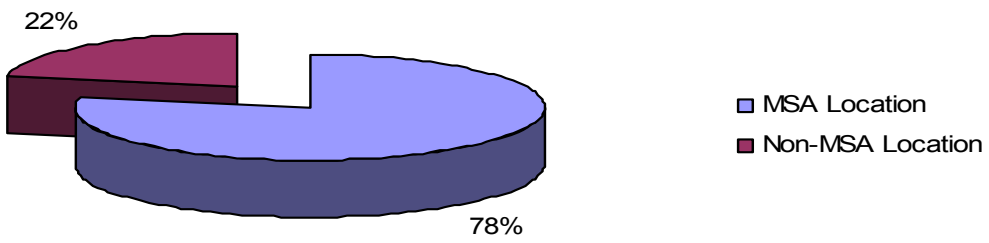
Figure 5.4: Years of education

The majority of the respondent population (95.3%) had at least a high school diploma. The respondent population is therefore educated and may find it less burdensome, cognitively to complete the telephone survey, enhancing the validity of the results obtained from this study.



N = 538

Figure 5.5: Annual household income



N = 538

Figure 5.6: MSA location

5.2 Random Effects Logistic Regression Model Estimation

The correlated nature of the binary outcome data, which represented the responses of participants to each of the16 items, necessitated the use of a random effects logistic regression model. The substantive and statistical significance of the logistic regression models can be estimated by the pseudo R2 measure and the maximum likelihood ratio test, respectively. (Menard, 1995) The logistic regression coefficients for the full model were obtained initially by adding all of the treatment attributes and sociodemographic variables of interest into the model. Similarly, coefficients for the nested models were then obtained. The first nested model contained only the treatment attributes while the second nested model contained only the sociodemographic variables. The magnitude and direction of coefficients were assessed for all models.

5.2.1 Model Estimation Results

Table 5.1 presents the results of the full random effects logistic regression model. The full model contained the following treatment attributes: efficacy, risk of side effects, dosage and cost. The sociodemographic characteristics entered into the model included age, gender, income, education and MSA status.

Table 5.1: Full Logistic regression model

Choice to Purchase a prescription for an ACEI

	Coef	Std Error	z	P > |z|	[95% Conf. Interval]	
Efficacy	.7732696	.059269	13.05	0.000	.6571045	.8894347
Side Effects	-2.66545	.0681524	-39.11	0.000	-2.799026	-2.531873
Dosage	-.9182781	.0597702	-15.36	0.000	-1.035426	-.8011307
Cost	-.0148639	.0019487	-7.63	0.000	-1.035426	-.8011307
Age	-.0116941	.0047429	-2.47	0.014	-.0209901	-.0023982
Gender	-.1535066	.1525512	-1.01	0.314	-.4525015	.1454882
Income	.0699604	.0381459	0.067	0.071	-.0048041	.1447249
Education	-.0808635	.043528	-1.86	0.063	-.1661769	.0044499
MSA	.0739335	.1741289	0.42	0.671	-.2673529	.41522
Constant	4.48557	.5789053	7.75	0.000	3.350937	5.620204

Likelihood-ratio test of rho=0: chibar2 (01) = 1279.72 Prob >= chibar2 = 0.000

Table 5.1 demonstrates that the absolute value of the risk of side effects treatment attribute coefficient had the greatest magnitude. The dosage schedule coefficient had the next highest level followed by the efficacy and the cost coefficients.

This means that respondents considered the risk of side effects associated with the ACEIs as the most important attribute in treatment decision making, followed by dosage convenience, efficacy, dosage and cost in that order. The introductory preface which was read to respondents at the beginning of the telephone interview defines the general side effects as the risk of headache, dizziness, fatigue and dry cough associated with the ACEIs (See Table 4.1).

This information is useful for clinicians because it suggests that the side effect profile of antihypertensive agents is of paramount importance to patients when they contemplate taking medicines. The physician may therefore focus on providing counseling to patients regarding the side effect profiles of prescribed antihypertensive agents and in addition, allay the concerns of patients regarding these side effects. From the results of this study, the dosage schedule is the next most important attribute of antihypertensive treatment. This information is of value to physicians because it suggests that patients prefer ACEIs and other antihypertensive agents with once daily dosage schedules.

The results of this research also suggests that the efficacy of antihypertensive agents, although important to patients, is less important compared to the side effect profile and the dosage schedule. Patients may assume intuitively, that antihypertensive agents have inherent efficacy and patients may consider other treatment attributes more closely in the treatment decision making process. This may impact long term adherence with therapy.

5.2.2 Theoretical Validity

The coefficients associated with the treatment attributes also exhibited theoretical validity as expected a priori. For instance, the efficacy attribute coefficient is significant and positive in direction. This means that as the efficacy level of the ACEIs increase, the likelihood of patient treatment choice with the ACEIs also increase. The risk of side effects attribute coefficient had a negative sign and is also significant. This may be interpreted intuitively that as the risk of the side effects associated with the ACEIs increases, the likelihood of patient treatment choice with the ACEIs decreases.

The dosage schedule attribute coefficient is negative and significant, indicating that as the dosage schedule becomes less convenient or as the number of doses taken per day increases, the likelihood of patient treatment choice decreases. The cost attribute is negative and significant, which means that as the co-payment cost of obtaining the ACEI prescription increases, the likelihood of patients to make treatment related choices decreases. The intercept term is positive and significant, indicating that, on the whole, respondents would choose treatment with the ACEIs (See Table 5.1). This information is important clinically because, it indicates that patients behave in theoretically hypothesized ways.

The directions of the coefficients of the sociodemographic variables were not specified a priori. The preference assessment literature suggests that the sociodemographic variables have not been consistently associated with preferences for treatment decision-making or treatment choice (Say, Murtagh & Thompson, 2006). For the current study, the age coefficient is negative (-0.01) indicating that as age increases, the likelihood of treatment choice with the ACEIs decreases.

The gender coefficient is negative, (-0.15) indicating that males were more likely to choose treatment with the ACEIs. The coefficient for income is positive, (0.07) indicating that, as income increases, the likelihood of treatment choice with the ACEIs also increases. The education coefficient is negative, (-0.08) indicating that as the level of education increases, the likelihood of treatment choice with the ACEIs decreases. Lastly, the MSA status coefficient is positive, (0.07) indicating that respondents living in non-MSA locations were more likely to choose treatment with the ACEIs compared to individuals living in MSA locations.

5.3 Results of Maximum Likelihood Ratio Test

A maximum likelihood ratio (MLR) test was also performed according to the procedure outlined by Menard (1995) and Hosmer and Lemeshow (1989). The likelihood ratio tests are useful to assess the statistical significance and the effects of groups of predictors on the dependent variable. A statistically significant maximum likelihood ratio test indicates that collectively, the variables in a nested model are important predictors of the dependent or outcome variable. The full logistic regression model with estimates of the effects of the attributes of the ACEIs (efficacy, adverse event profile, dosage schedule and cost of therapy) as well as the sociodemographic variables was initially fitted [full model].

Two models [nested models] estimating the effect of the treatment attributes of the ACEIs on the probability of treatment choice and the effect of the sociodemographic variables on treatment choice were subsequently fitted. The MLR test was performed by initially saving the likelihood of the MLR test in a user-defined variable (M1). The nested model with the treatment attributes was then fitted followed by a STATA command

(lrtest M1) to evaluate the MLR test. Table 5.4 shows that, collectively, the treatment attributes are significant predictors of patient treatment choice with the ACEIs based on the significant p-value (0.0232) associated with the treatment attributes model.

Similarly, the nested model containing only the sociodemographic variables was fitted. The STATA command (lrtest M1) was also used to evaluate the MLR test. Table 5.9 shows that, collectively, the sociodemographic variables are significant predictors of patient treatment choice with the ACEIs based on the significant p-value (<0.001) associated with the sociodemographic variables model. The results of the MLR tests indicate that separately, both the treatment attributes and the sociodemographic variables are significant predictors of treatment choice for the ACEIs. Tables 5.2 and 5.3 show the coefficients associated with each of the models.

Table 5.2: Model Coefficients (Treatment attributes)

Choice to Purchase a prescription for an ACEI

	Coef	Std Error	z	P > |z|	[95% Conf.	Interval]
Efficacy	.7757023	.059305	13.08	0.000	.6594666	.891938
Side Effects	-2.668385	.0682221	-39.11	0.000	-2.802098	-2.534673
Dosage	-.9190743	.0597984	-15.37	0.000	-1.036277	-.8018716
Cost	-.0148726	.0019495	-7.63	0.000	-.0186936	-.0110516
Constant	3.865298	.1811585	21.34	0.000	3.510234	4.220362

Likelihood-ratio test of rho=0: chibar2 (01) = 1328.24 Prob >= chibar2 = 0.000

Table 5.3: Model Coefficients (Sociodemographic variables)

Choice to Purchase a prescription for an ACEI

	Coef	Std Error	z	P > |z|	[95% Conf.	Interval]
Age	-.0081819	.0033211	-2.46	0.014	-.0146912	-.0016726
Gender	-.0979326	.1074143	-0.91	0.362	-.3084608	.1125955
Education	-.0569537	.0305822	-1.86	0.063	-.1168938	.0029863
Income	.0486704	.026923	1.81	0.071	-.0040978	.1014386
MSA	.0407877	.1235427	0.33	0.741	-.2013516	.2829269
Constant	-.0673519	.3887384	-0.17	0.862	-.8292651	.6945613

Likelihood-ratio test of rho=0: chibar2 (01) = 759.12 Prob >= chibar2 = 0.000

5.4 Pseudo R2 Values

The pseudo R2, a measure of the substantive significance of the random effects logistic regression model, was calculated using the STATA output. The Pseudo R2 measure is analogous to the R2 measure in multiple or ordinary least squares regression, which is interpreted as the amount of variance explained by the model. The pseudo R2 was calculated for each model by initially running a nested model containing only the constant or intercept value and obtaining the log likelihood of this model. The log likelihoods of the full models containing the treatment attributes, the sociodemographic variables or the full model containing the combination of the treatment attributes and sociodemographic variables were then obtained as well. The pseudo R2 value was obtained from the formula below:

Pseudo R2 = LL (constant only model) – LL (full model) / LL (constant only model). Table 5.9 presents the pseudo R2 values of the full models.

Table 5.9 shows that the full model containing the treatment attributes and the sociodemographic variables explained 22.91% of the variance associated with the dependent variable. The full model containing the treatment attributes alone, explained 22.79% of the variance associated with the dependent variable. The full model containing the sociodemographic variables alone explained only 0.12% of the variance associated with the dependent variable. Table 5.9 suggests that other, unmeasured variables may further explain or predict treatment choice with the ACEIs. The result of the pseudo R2 calculations also suggests that the sociodemographic variables make little contribution to the prediction of treatment choice with the ACEIs. However, the treatment attributes explain the majority of the variance associated with the dependent variable.

5.5 Results of Tests of Hypotheses

The full random effects logistic regression model facilitates the tests of hypotheses outlined in Chapter 3. The model establishes whether or not treatment attributes and sociodemographic variables have an effect on treatment choice with the ACEIs. The first hypothesis pertained to the existence of an effect or otherwise, of efficacy on treatment choice with the ACEIs.

Ho $_1$ Perceived efficacy of treatment has no effect on patient choice of treatment with the ACEIs.

The model indicated that the efficacy coefficient was significant (p-value > 0.001). Therefore, this null hypothesis was rejected (See Table 5.1). The second hypothesis related to the risk of adverse events or the side effect attribute.

Ho $_2$ Risk of adverse events has no effect on patient choice of treatment with the ACEIs.

The model indicated that the side effect coefficient was significant (p-value > 0.001). Therefore, this null hypothesis was rejected. The third hypothesis addressed the effect of the dosage schedule attribute of the ACEIs on patient treatment choice.

Ho $_3$ Dosage schedule has no effect on patient choice of treatment with the ACEIs.

The model indicated that the dosage schedule coefficient was significant (p-value > 0.001). Therefore, this null hypothesis was rejected. The fourth hypothesis pertained to the effect of the cost of therapy attribute of the ACEIs on patient treatment choice.

Ho $_4$ Cost of therapy has no effect on patient choice of treatment with the ACEIs.

The model indicated that the cost of therapy coefficient was significant (p-value > 0.001). Therefore, this null hypothesis was rejected. The fifth hypothesis related to the effect of the demographic variable, age, on patient treatment choice with the ACEIs.

Ho $_5$ Age has no effect on choice to purchase antihypertensive therapy with the ACEIs; there is no difference in choice to purchase antihypertensive therapy between patients younger than 65 years of age and patients 65 years of age and older

The model indicated that the age coefficient was significant (p-value= 0.004). Therefore, this null hypothesis was rejected. The sixth hypothesis pertains to the effect of gender on patient treatment choice with the ACEIs.

Ho_6 Gender has no effect on choice to purchase antihypertensive therapy with the ACEIs; there is no difference in choice to purchase antihypertensive therapy between male and female patients.

The model indicated that the gender coefficient was not significant at the 5% level of significance (p-value= 0.314). Therefore, this null hypothesis was not rejected. The seventh hypothesis related to the effect of income on patient treatment choice with the ACEIs.

Ho_7 household income has no effect on choice to purchase antihypertensive therapy with the ACEIs.

The model indicated that the income coefficient was not significant at the 5% level of significance (p-value = 0.071). Therefore this null hypothesis was not rejected. The eighth hypothesis pertained to the effect of education on patient treatment choice with the ACEIs.

Ho_8 Education has no effect on choice to purchase antihypertensive therapy with the ACEIs; there is no difference in choice to purchase antihypertensive therapy between patients with less than a college education and patients who have some or more college education.

The model indicated that the education coefficient was not significant at the 5% level of significance (p-value= 0.063). Therefore, this null hypothesis was not rejected.

The ninth hypothesis pertained to the effect of MSA status on patient treatment choice with the ACEIs.

Ho_9 MSA location has no effect on choice to purchase antihypertensive therapy with the ACEIs; there is no difference in choice to purchase antihypertensive therapy between patients living in MSA locations and patients living in non-MSA locations.

The model indicated that the Metropolitan Statistical Area (MSA) status coefficient was not significant at the 5% level of significance (p-value= 0.646). Therefore, this null hypothesis was not rejected (See Table 5.1).

5.6 Marginal Rate of Substitution (MRS) Analysis

A marginal rate of substitution is presented in Figure 5.7. According to Ryan & Gerard (2003), a marginal rate of substitution analysis may be performed by finding the ratio of 2 attributes of interest in order to estimate the rate at which respondents are willing to trade off attributes. In this case, the attributes of interest were the treatment attributes associated with the ACEIs. The denominator for our MRS analysis was the cost attribute which allowed the estimation of indirect WTP. Figure 5.7 shows the indirect WTP for improvements in the levels of efficacy, side effects and dosage convenience associated with the ACEIs.

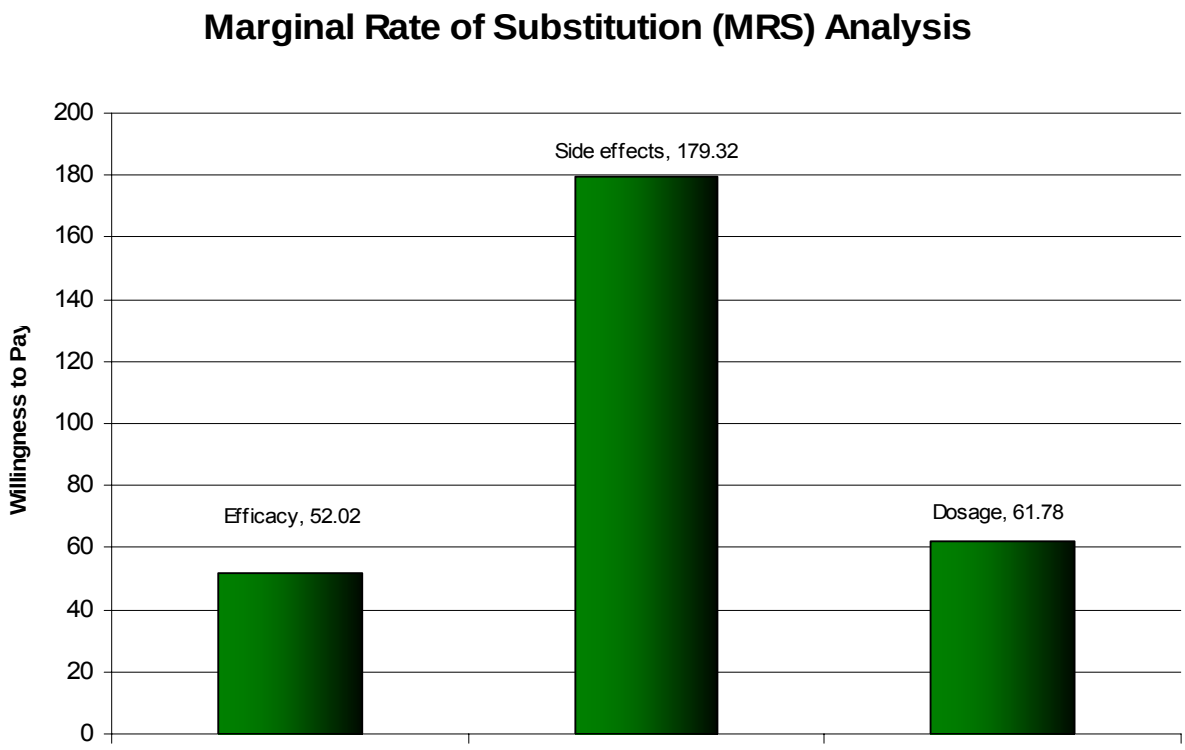


Figure 5.7: Marginal rate of substitution analysis

A marginal rate of substitution analysis may be used to generate indirect WTP estimates for improvements in the levels of treatment attributes. According to Ryan and Gerard (2003), a MRS analysis may be performed by finding the ratio between the treatment attribute coefficient and the cost coefficient. The value obtained is interpreted as the willingness to pay for improvement in the level of the treatment attribute. For instance, the results of the MRS analysis showed that respondents are WTP $179.32 per month for reduction from a high risk to a low risk of side effects associated with the ACEIs.

The results of the MRS analysis for the current study also showed that respondents were WTP $52.02 per month for improvement in efficacy from a slightly lower level of blood pressure reduction and target organ protection, to a slightly higher level of blood pressure reduction and target organ protection associated with the ACEIs. Respondents were WTP $61.78 per month for improvement in dosage convenience, that is, respondents are WTP this amount for moving from a dosage of three times a day to a once daily dosage.

Willingness to pay has been described as a measure of strength of preference. The results of the MRS analysis is important for clinicians and physicians because the willingness to pay estimates generated in the current study shows that respondents possess strong preferences for improvements in the levels of treatment attributes of the ACEIs. Although respondents may not in reality, pay the amounts generated as indirect willingness to pay for improvements, the relative magnitude of these amounts for each of the treatment attributes also suggests that, in order of decreasing importance, side effects, dosage schedule and efficacy of antihypertensive agents and the ACEIs in particular impact patient choice for ACEI therapy.

5.7 Attribute coefficients in various populations

The treatment attribute coefficients were investigated in various sub-populations and the relative importance of these attributes was compared in these sub-populations. For males and females, there were no differences in the relative importance of the treatment attributes. The order of importance of treatment attributes for both males and females was: side effects, dosage, efficacy and cost (Table 5.4).

Table 5.4: Attribute coefficients (Gender)

Treatment Attribute	Males (n=195) Coeff (s.e)	Females (n=343) Coeff (s.e)
Side effects	-2.32 (0.11)	-2.88 (0.09)
Dosage	-0.89 (0.09)	-0.94 (0.08)
Efficacy	0.87 (0.09)	0.73 (0.08)
Cost	-0.02 (0.00)	-0.01 (0.00)

For the age variable, there was also congruence in the relative importance of the treatment attributes between respondents 65 years or younger and respondents older than 65 years. The order of importance was the same for both populations. The order of importance of treatment attributes for both groups was side effects, dosage, efficacy and cost (Table 5.5).

Table 5.5: Attribute coefficients (Age)

Treatment Attribute	Age <=65 years (n=458) Coeff (s.e)	Age > 65 years (n=83) Coeff (s.e)
Side effects	-2.70 (0.07)	-2.44 (0.17)
Dosage	-0.91 (0.07)	-0.96 (0.15)
Efficacy	0.81 (0.06)	0.56 (0.15)
Cost	-0.02 (0.00)	-0.01 (0.00)

For the MSA status variable, there was a slight difference in the relative importance of attributes between respondents living in MSA locations versus individuals living in non-MSA locations (Table 5.6). The order of importance of treatment attributes for individuals living in MSA locations was side effects, dosage, efficacy and cost. For individuals living in non-MSA locations, the order of importance of treatment attributes was side effects, efficacy, dosage and cost, although there was only a slight difference in the magnitude of the efficacy and dosage attribute coefficients.

Table 5.6: Attribute coefficients (MSA status)

Treatment Attribute	MSA location (n=428) Coeff (s.e)	Non-MSA location (n=122) Coeff (s.e)
Side effects	-2.66 (0.08)	-2.68 (0.15)
Dosage	-0.92 (0.07)	-0.89 (0.13)
Efficacy	0.74 (0.07)	0.90 (0.13)
Cost	-0.01 (0.00)	-0.02 (0.00)

For the income variable, there was no difference in the relative importance of the treatment attributes between respondents with household incomes below $50,000 per annum and respondents with incomes greater than $50,000 per annum. The order of importance for both income groups was: side effects, dosage, efficacy and cost (Table 5.7).

Table 5.7: Attribute coefficients (Income)

Treatment Attribute	Income (<$50,000) (n=273) Coeff (s.e)	Income (>=$50,000) (n=269) Coeff (s.e)
Side effects	-2.58 (0.09)	-2.75 (0.09)
Dosage	-0.77 (0.08)	-1.07 (0.08)
Efficacy	0.72 (0.08)	0.82 (0.08)
Cost	-0.02 (0.00)	-0.01 (0.00)

For the education variable, there were differences in the relative importance associated with treatment attributes between respondents with a college education or less (side effects, dosage, efficacy and cost) and respondents with greater than a college education (side effects, efficacy, dosage and cost) [Table 5.8].

Table 5.8: Attribute coefficients (Education)

Treatment Attribute	College education or less (n=298) Coeff (s.e)	Greater than a college education (n=244) Coeff (s.e)
Side effects	-2.72 (0.09)	-2.64 (0.10)
Dosage	-0.82 (0.08)	-1.04 (0.09)
Efficacy	0.47 (0.08)	1.13 (0.09)
Cost	-0.019 (0.00)	-0.01 (0.26)

Table 5.9: Coefficients for Full and Nested Models

Choice to purchase a prescription for an ACEI

	Full Model (A) Coefficients		Treatment Attributes Model (B) Coefficients		Sociodemographic Variables Model (C) Coefficients
Efficacy	.7732696*	Efficacy	.7757023*	Age	-.0081819*
Side Effects	-2.66545*	Side Effects	-2.668385*	Gender	-.0979326
Dosage	-.9182781*	Dosage	-.9190743*	Income	.0486704
Cost	-.0148639*	Cost	-.01487268*	Education	-.0569537
Age	-.0116941*	Constant	3.865298	MSA	.0407877
Gender	-.1535066			Constant	-.0673519
Income	.0699604				
Education	-.0808635				
MSA	.0739335				
Constant	4.48557				
	Log Likelihood		Likelihood-ratio test		Likelihood-ratio test
Constant only model	-5399.9196	*Pseudo R2*	LR chi2 (5) = 13.02 Prob > chi2 = 0.0232		LR chi2 (4) = 2462.81 Prob > chi2 = 0.0000
Full model (A)	-4162.7113	0.2291			
Full model (B)	-4169.3997	0.2279			
Full model (C)	-5393.1825	0.0012			

* = $p<0.05$

CHAPTER 6

DISCUSSION AND CONCLUSION

6.1 Discussion and study results

To the best of our knowledge, this study is the first to assess the relative importance of antihypertensive drug (ie the ACEIs) attributes using a discrete choice experiment. The treatment attributes examined included: efficacy, risk of side effects, dosage schedule and cost. In addition, this study was the first to evaluate the monetary value, as determined by indirect willingness to pay, that patients place on improved efficacy, simpler dosage regimens and reduced risk of adverse events of the ACEIs. The willingness to pay estimates obtained from this study may also be incorporated into a future cost benefit analysis. Furthermore, unlike direct willingness to pay studies that yield only monetary estimates of willingness to pay for improvements in attribute levels, discrete choice experiments, like this study, yield both utilities and indirect willingness to pay estimates. Discrete choice experiments also indicate the relative importance of the attributes of multi-attribute goods and services.

A major finding of the current study that assessed the ACEI antihypertensive drugs indicate that patients are willing to participate in treatment decision-making in the treatment of hypertension. The inclusion of patient preferences in their treatment has the potential to improve compliance and other health outcomes (Bernardini, 2004; Bowling & Ebrahim, 2001). The following treatment attributes are important

considerations for treatment with the ACEIs: efficacy, risk of side effects, dosage schedule and the costs associated with ACEI therapy.

The results of this study indicate that the side effect profile of the ACEIs is the most important determinant of treatment decision-making in this group of respondents, consisting of individuals with and without hypertension. The decreasing order of importance of the other treatment attributes of the ACEIs was dosage schedule, efficacy and cost, in that order. The treatment attributes predicted approximately 22% of the variance associated with the dependent variable, choice to purchase a prescription for the ACEIs. Treatment attributes collectively had a predictive efficiency of about 22% and this suggests that other predictors of treatment choice exist and need to be included in the logistic regression equation. Some of these other predictors of treatment choice may include disease severity, the level of trust that patients have in their physicians and physician communication style.

The sociodemographic variables, age, gender, income, education and MSA status, as a group, also predicted choice to accept treatment with the ACEIs. However, except for age, the sociodemographic variables individually did not significantly predict treatment decisions as determined by choice to accept treatment with the ACEIs. The preference assessment literature suggests that the relationship between sociodemographic variables and patient preferences for treatment decision making is equivocal (Say et al., 2006; Haynes, 1979). The lack of a significant effect of the sociodemographic variables on patient preferences for the ACEIs was therefore, not unanticipated.

The results of the marginal rate of substitution analysis suggest that respondents have strong preferences for improvements in the levels of the efficacy, risk of side effects and dosage schedule attributes. The strength of preference of respondents may be gauged by the magnitude of indirect willingness to pay for improvements in the levels of ACEI attributes. Respondents were willing to pay $ 179.32 per month for improvement in the side effect profile of the ACEIs from a high to a low risk of general side effects (headache, dizziness, fatigue and dry cough. Respondents were also willing to pay $61.78 per month for improvement in the dosage schedule from three times daily to once daily. Lastly, respondents were willing to pay $52.02 per month for improvement in efficacy from a slightly lower level of efficacy to a slightly higher level of efficacy. The indirect willingness to pay estimates for improvements in the levels of the efficacy, side effect and dosage schedule treatment attributes were generated by finding the ratio of the treatment attribute coefficient and the cost coefficient. The resulting estimate is the indirect willingness to pay for improvement in the attribute level.

The indirect willingness to pay estimates represents aggregates of strength of preference for the components of the efficacy and side effect attributes. For instance, the efficacy attribute was defined for this study as consisting of blood pressure lowering and target organ protection capability. Similarly, the side effect attribute was defined as the risk of developing headaches, dizziness, fatigue and dry cough associated with the administration of the ACEIs. An alternative approach would have been to obtain willingness to pay estimates for the blood pressure lowering and target organ protection effect separately, as well as obtaining willingness to pay estimates for avoidance of each of the side effects of the ACEIs separately.

The alternative approach was not taken in order to reduce respondent burden. The total number of attributes considered for this study was limited to four. The number of attributes was also limited due to the telephone survey mode of administration which may present cognitive challenges to respondents, some of whom are elderly. The efficacy attribute, therefore, comprised a composite of the effect of the ACEIs on blood pressure lowering as well as the effect of the ACEIs on target organ protection. Similarly, the side effect attribute comprised a composite of side effects associated with the ACEIs. Future research should examine the impact of blood pressure control separately from the impact of target organ protection on patient preferences for antihypertensive therapy. Similarly, the effect of individual side effects on patient preferences for antihypertensive therapy should be examined.

Subgroup analyses revealed that the relative importance of ACEI treatment attributes did not differ across gender, age (younger or equal to 65 years versus older than 65 years) nor income levels (income less than $50,000 versus income greater than or equal to $50,000). The $50,000 amount was selected as the break point to classify the population into income levels because about 50% of the respondent population, consisting of residents of the State of Georgia, has annual household incomes above and below $50,000. The decreasing order of relative importance of ACEI attributes for these three demographic variables was side effects, dosage schedule, efficacy and cost as determined by the magnitude of statistically significant attribute coefficients. However, there was a difference in the relative importance of ACEI attributes for respondents living in MSA locations compared to respondents living in non-MSA

locations. There was also a difference in the relative importance between individuals with a college education or less versus individuals with greater than a college education.

The decreasing order of importance of treatment attributes for individuals living in MSA locations was side effects, dosage, efficacy and cost. For individuals living in non-MSA locations, the decreasing order of importance of treatment attributes was side effects, efficacy, dosage and cost, although there was only a slight difference in the magnitude of the efficacy and dosage attribute coefficients. This indicates that individuals living in MSA locations, which are contiguous areas of high population density, consider dosage schedule more important than the efficacy level of the medication. The lifestyle of individuals living in MSA locations may not encourage adherence to complex drug dosage regimes and individuals living in MSA locations may therefore prefer medications with less complex dosage regimes compared to individuals living in non-MSA locations.

For the education variable, the order of importance associated with treatment attributes between respondents with a college education or less was side effects, dosage, efficacy and cost and for respondents with greater than a college education, the decreasing order of importance associated with treatment attributes was side effects, efficacy, dosage and cost. Therefore, individuals with greater than a college education considered efficacy more important than the dosage schedule of the ACEIs. This finding suggests that the dosage schedule is less of a concern to patients with greater than a college education and this group of patients could be more concerned about the efficacy level of the antihypertensive drug. They may want more information regarding how antihypertensive drugs work and the benefits offered by the various

alternative antihypertensive drugs and may be willing to adhere to complex dosage regimes, so long as the treatment is perceived to be effective.

Having adequate health insurance to cover the costs of prescription drugs may explain the consistent finding that cost was relatively unimportant for respondents. The co-payment levels ($10 per month and $40 per month) may also be affordable to patients who may consider other attributes such as the risk of side effects, efficacy levels and dosage schedule more important, compared to the cost of therapy.

Preferences for antihypertensive therapy have been investigated previously. Some of these studies have used a qualitative approach (Ogedegbe et al., 2004; Morecroft et al, 2006). Other studies have used willingness to pay approaches that did not employ the profiles of specific antihypertensive agents such as the ACEIs (Johannesson et al., 1991; Ramsey et al., 1997). Willingness to pay studies, provide important information about the strength of patient preferences for interventions or attributes of interventions and provide monetary estimates of benefit. These estimates may then be used in cost benefit analyses to determine the feasibility of programs or healthcare interventions.

The validity of direct willingness to pay studies is a subject of debate in the preference assessment literature (Mitchell & Carson, 1989). The debate has centered on the truthfulness of direct willingness to pay estimates. Willingness to pay estimates obtained under hypothetical conditions or scenarios may not always equate with actual willingness to pay amounts. Respondents may therefore overstate willingness to pay amounts (Mitchell & Carson, 1989). Willingness to pay studies are also prone to various types of biases including a lack of scope sensitivity or the lack of sensitivity of the

monetary estimates to the size of the program on offer. Other biases include implied value cues such as starting point bias and range bias. Starting point bias is associated with the bidding game willingness to pay elicitation format while range bias is associated with the payment card format and these kinds of biases influence the final willingness to pay estimates elicited (Mitchell & Carson, 1989).

Discrete choice experiments offer several advantages over the willingness to pay approach. First of all, discrete choice experiments can provide two kinds of preference measures, estimates of willingness to pay as well as utilities associated with interventions and the attributes of interventions. Secondly, discrete choice experiments can be used to assess the relative importance of attributes of interventions and to examine the trade-offs that respondents make when they value multiattribute interventions or goods and services. Furthermore, reports on the validity of discrete choice experiments have been positive (Ryan & Gerard, 2003; Ryan 1999).

Discrete choice experiments have not been associated with the biases commonly linked to willingness to pay studies such as a lack of sensitivity to scope. A lack of sensitivity to scope refers to the direct willingness to pay estimates obtained not being reflective of the size of the program or the intervention on offer. Therefore, the current study used a discrete choice experiment to investigate the preferences for a specific class of antihypertensive agent, the ACEIs. The results of the current study provide further evidence for the validity of the discrete choice experiment in the measurement of patient preferences.

The evidence for the validity of the discrete choice experiment increases because of its use in hypertension, an important chronic disease. Discrete choice

experiments have been employed in other chronic diseases such as HIV and benign prostatic hypertrophy with evidence of theoretical and internal validity (Beusterien et al, 2005). Therefore, the application of a discrete choice experiment to examine the nature of patient preferences for antihypertensive therapy will provide further evidence for the validity of the discrete choice experiment in the measurement of patient preferences. Theoretical validity is evident when concepts behave in previously hypothesized ways. For instance, theoretically, treatment choice is expected to decrease with higher cost, higher incidence of side effects and lower efficacy levels. Therefore, the application of a discrete choice experiment to examine the nature of patient preferences for antihypertensive therapy will provide further evidence for the validity of the discrete choice experiment in the measurement of patient preferences.

6.2 Clinical significance

The clinical implications of the results of this study are worthy of note. The findings of this study that overall, patients are willing to participate in treatment decision-making regarding the choice to purchase a prescription for an ACEI represent an important way to improve patient care. For instance, treatment guidelines such as the JNC 7 report suggest that patients should be involved in treatment decision-making (Chobanian et al., 2003). Our study confirms this. An important way to involve patients in their own care may be to elicit and incorporate patient's preferences into treatment decision-making. Consideration of the treatment preferences of patients by physicians may result in improved quality of care, patient satisfaction with treatment and improved health outcomes (Bernardini, 2004; Bowling& Ebrahim, 2001).

Patients who are willing to participate in treatment decision making related to ACEI or other anti-hypertensive medication may require information on the efficacy, side effects, dosage schedule and cost attributes of the medication and physicians are well positioned to provide information on the attributes and the risks and benefits of antihypertensive therapy. Because of increasingly limited consultation times between physicians and patients, other health care professionals such as pharmacists may also be in a good position to offer medication related counseling to patients.

The provision of this information by physicians to patients and the treatment preferences expressed by the patient may translate to improved adherence levels. The inclusion of patient preferences in treatment decision making may also lead to increased levels of adherence. Improved levels of adherence will enhance treatment success, reduce the incidence of hospitalization for complications of hypertension and in the process, reduce the overall social and economic cost burden associated with chronic hypertension.

It is important to include the preferences of patients for antihypertensive therapy in the context of the physician patient interaction because the treatment preferences of physicians and patients may not always align. Physicians may assume that they know their patients' preferences for antihypertensive therapy without asking these patients directly. On the other hand, patients may be reluctant to share their concerns or perceived barriers to adherence to therapy such as an inability to afford the prescribed medication with their physicians. Improved communication between physicians and patients will translate into improved health outcomes for patients because patients'

preferences may be incorporated into the treatment selected (Bowling & Ebrahim, 2001; Bernadini, 2004).

The results of this research have important implications for patient education programs. These programs, encouraging patients to adhere to antihypertensive medication as a way to improve blood pressure control may focus on messages allaying the concerns of patients regarding the side effects of antihypertensive therapy and the risk of developing these side effects. Patient education about side effects of antihypertensive therapy may also include information regarding how to recognize rare, but important side effects associated with antihypertensive therapy and what to do if these side effects occur.

The finding of this study that side effect profile is the most important attribute considered by respondents in treatment decision making with the ACEIs is important because it provides a springboard for the discussion of the attributes of ACEI treatment with patients by physicians. Shortened consultation times often constrain the physician patient interaction and on the other hand, physicians have been urged to provide more information regarding the disease and the prescribed treatment to patients. There may be a need therefore, to prioritize the information presented to patients.

The information presented to patients may be enhanced by the use of decision aids. Decision aids may also be incorporated into the clinical consultation to explain difficult concepts associated with the disease or its treatment. Information regarding the side effects of various treatment alternatives may be presented to patients first, before information on the other treatment attributes are presented. It's interesting to note that the efficacy attribute was not the most important attribute considered by patients in

treatment decision-making. This may be due to patients having an innate confidence that the antihypertensive agent will be efficacious after having passed through the regulatory and drug approval process.

The efficacy, risk of side effect, dosage schedule and cost profiles of the currently available ACEIs (Captopril, Enalapril, Benazepril, Fosinopril, Lisinopril, Quinapril, Moexipril, Perindopril, Ramipril and Trandolapril) were reviewed in order to design the attributes and levels presented to patients. The ACEI class of antihypertensive agents has been shown to provide target organ protective effects independent of their blood pressure lowering effects (Toto et al., 2004). ACEIs have been shown to be effective agents in the treatment of hypertension, heart failure and nephropathy (Vuong & Annis, 2003) Therefore, patients with hypertension who are at risk of other cardiovascular diseases or who have concomitant cardiovascular diseases such as congestive heart failure may benefit from treatment with the ACEIs.

The results of this study indicate that the decreasing order of importance of the ACEI attributes is: risk of side effects, dosage schedule, efficacy and cost. Respondents would prefer ACEIs with a low risk of general side effects, convenient once daily dosage, higher levels of efficacy as measured by blood pressure lowering effect and target organ protection and finally low cost. Based on this finding, ACEIs such as Ramipril and Trandolapril which are effective well tolerated may be taken once daily and which are comparable in cost to the other ACEIs, should be considered for formulary inclusion. In addition to its proven effectiveness in the treatment of hypertension, heart failure and nephropathy, Ramipril has been shown to prevent cardiovascular events such as myocardial infarctions, strokes and cardiovascular deaths in high-risk patients

who do not present with left-ventricular dysfunction or heart failure (Vuong & Annis, 2003).

Currently, only a few health plans in Georgia list Ramipril (Altace ®, Renaphro ®) on their formularies. Those health plans that list Ramipril on their formularies place restrictions such as limits on the quantity of the medication that may be dispensed over a time frame. Other restrictions applied for Ramipril include step therapy which precludes the use of brand alternatives until treatment with a generic alternative has been tried unsuccessfully. The beneficial effects and profiles of Ramipril and other ACEIs such as Trandolapril with limited formulary inclusion in health plans in Georgia should be considered by health plan administrators with a view to revising these formularies to include Ramipril and other ACEIs with beneficial therapeutic profiles.

6.3 Limitations and considerations for future research

This study utilized a discrete choice experiment, a stated preference assessment technique which typically employs hypothetical scenarios. The responses of participants obtained under hypothetical scenarios may not represent the behavior of these respondents in real life. This may be contrasted with information obtained from revealed preference data which describes actual behavior. An example of revealed preference data is contained in retrospective databases which includes information on previous health consumption and past healthcare behavior.

The use of hypothetical patients to obtain stated treatment preferences for choice of treatment with the ACEIs represents another limitation of this study. Respondents were asked to assume that they had hypertension if they were not currently hypertensive. Although some of the respondents may be hypertensive, there was no

item included to identify hypertensive and non-hypertensive patients. The impact of experience with hypertension on choice to purchase a prescription for an ACEI therefore, was not assessed in this study.

The results of this study is also limited by the cross sectional nature of the data. The preference assessment literature suggests that patient preferences may change with time (Say et al., 2006). However, the fact that the data for this study was collected at one time did not allow the examination of temporal trends that may exist in the data with regards to the nature of preferences for ACEI therapy among various population subgroups. Furthermore, although data collection was supervised and conducted using several trained interviewers, there is the possibility that interviewer bias may have impacted the results of this study. Interviewer bias may introduce systematic variance or error into the data collected. Regular quality control checks and interviewer audits were employed in order to reduce the level of interviewer bias.

The generalizability of the results of this study is limited. Data was collected from the State of Georgia and the findings of this study may only be limited to the target population of adults in Georgia with telephones. It is possible that the behavior of respondents in other states of the US may be different from the behavior of respondents in the State of Georgia. Therefore, a nationally representative sample represents an important next step for this study.

Furthermore, the telephone sampling and survey methodology is associated with various disadvantages which include limited interview times, the inability to employ visual aids to explain difficult concepts and the challenges associated with locating individuals who are willing and able to complete the telephone interviews. Future

research should utilize in-person surveys or other survey methods and the findings of such studies may be compared to the findings of the current study. Future research using other survey methods should be completed in order to learn more about the effect of survey method on patient preferences for antihypertensive therapy.

The first step in the conduct of a discrete choice experiment involves the identification and selection of attributes and levels associated with the intervention, in this case, the ACEIs. For the current study, we identified the attributes and levels associated with the ACEIs through a review of the literature. The preference assessment literature identifies the use of qualitative research techniques such as focus groups and the use of expert opinion as other approaches for the establishment of attributes and levels for discrete choice experiments. It is possible that the use of any of these approaches for the identification of attributes and levels may result in different attributes and levels, which may subsequently impact the results obtained. The subjective nature of attribute selection and identification of levels of these attributes may exclude several important attributes which may determine preferences for the ACEIs.

The efficacy attribute of the ACEIs was defined as the ability to reduce blood pressure and improve target organ protection. The efficacy attribute was defined in terms of blood pressure lowering effect and target organ protection in order to reduce the cognitive burden associated with the administration of the survey over the telephone. It may have been more valid to investigate the impact of blood pressure lowering ability on patient preferences for the ACEIs separate from the ability of the ACEIs to provide target organ protection. This may have been achieved with the use of several efficacy attributes simultaneously instead of a single efficacy attribute. The

current study did not employ several efficacy attributes because of the need to consider the cognitive burden that may be associated with responding to telephone surveys. Similarly, in order to reduce respondent burden on the telephone, the risk of side effects profile of the ACEIs was defined using a combination of various side effects associated with the ACEIs. The side effects include headache, dizziness, fatigue and dry cough. It may also be interesting to investigate the impact of each ACEI side effect on patient preferences or choice to purchase an ACEI, separately. A future study may therefore investigate the impact of individual side effects and separate efficacy attributes on patient preferences for the ACEIs as well as other antihypertensive agents.

The current study examined the preferences of respondents for choice to purchase antihypertensive therapy using only one class of agents: the ACEIs. The ACEIs are an important class of antihypertensive agents, but there are other important classes of antihypertensive agents such as the diuretics, beta-blockers and the angiotensin receptor blockers (ARBs). The results of this study may also apply to antihypertensive agents with a similar profile to the ACEIs such as the ARBs. Future research may investigate the nature of patient preferences for these other classes of antihypertensive agents. Future research may also investigate the nature of patient preferences for combination antihypertensive therapy. The nature of patient preferences especially the relative importance of treatment attributes for monotherapy as well as combination therapy may be compared in a future study.

The attributes of combination therapy and the profiles of the medications making up the combination therapy may impact patient reference in important, but yet, unresearched ways. The current study elicited preference information only from

patients. There are other important stakeholders in the health care system such as physicians, caregivers and policymakers and it is likely that the relative importance of ACEI treatment attributes in these other populations may differ from the results of this study. Although the elicitation of patient preferences and the inclusion of these preferences in treatment decisions facilitate shared treatment decision-making, the physician and other stakeholders in the healthcare environment also play an important part in treatment decision-making. The exploration of the preferences of physicians, family members, caregivers and other stakeholders for ACEI treatment attributes may represent an important focus for future research.

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Appendix

Randomized items for the Georgia Poll administration

Q1. So for instance, if the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs 40 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q2. If the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects, costs 10 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q3. If the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects, costs 40 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q4. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects, costs 40 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q5. If the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects,

costs 40 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q6. If the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs 40 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q7. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects, costs 10 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q8. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects, costs 40 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q9. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs 40 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q10. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs

10 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q11. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects, costs 10 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q12. If the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs 10 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q13. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs 10 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q14. If the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a high risk of causing general side effects, costs 10 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q15. If the drug had a slightly lower chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs 10 dollars every month, and the dosage is once a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained

Q16. If the drug had a slightly higher chance of reducing high blood pressure and protecting the heart and kidneys, a low risk of causing general side effects, costs 40 dollars every month, and the dosage is three times a day, would you take the prescribed drug?

1. Yes
2. No

- Refused
- Don't know
- Not ascertained