With universal immunization, better health care infrastructure, and improved sanitation, aided by economic transition, there is perceptible shift in India’s major killers from infectious diseases to lifestyle diseases such as hypertension, cardiovascular diseases and diabetes. Today, hypertension is emerging as a major public health problem (Patnaik et al., 2007) and India is heading towards becoming the “Hypertension Capital of the World” (Joshi et al., 2007).

In the year 2000, nearly one billion people, roughly 26% of the adult population, had hypertension worldwide and this is predicted to increase to 1.56 billion by 2025 (Kearney et al., 2005). However, the prevalence varies markedly in different regions with rates as low as 3.4% (men) and 6.8% (women) in rural India and as high as 68.9% (men) and 72.5% (women) in Poland. The prevalence of hypertension has remained stable or has decreased in economically developed countries during the previous decade, while it has increased in developing countries (Kearney et al., 2004).

In the same year, 16.7 million people died from cardiovascular diseases, accounting for 30.3% of all deaths worldwide. More than half these deaths were in the developing countries. South Asia (Pakistan, India, Bangladesh, Nepal, Sri Lanka) represents more than a quarter of the developing world. Deaths from coronary heart disease in India rose from 1.17 million in 1990 to 1.59 million in 2000 and were expected to rise to 2.03 million in 2010 (Yadav et al., 2008).

Hypertension, a chronic elevation of blood pressure beyond levels known to increase the risk of CVD-related morbidity and mortality, is known to be caused by an interaction of intravascular volume, cardiac output and peripheral resistance. It is a major risk factor in the development of cardiovascular diseases. People with hypertension are known to have a two-fold higher risk of developing coronary artery disease, four times higher risk of congestive heart failure and seven times higher risk of cerebrovascular disease and stroke compared to people with normal blood pressure (Stamler, 1991).

Essential hypertension is a heterogeneous group of diseases with a common end result of elevated blood pressure (BP). The definition of hypertension has varied
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internationally, as well as over time, which has been an obstacle in epidemiological studies when assessing prevalence. A meta-analysis of hypertension prevalence rates in India (Gupta, 1997) demonstrated a significant increase in the prevalence. The prevalence varies considerably from one region to another. Sporadic studies from different parts of the country provide data on the epidemiological study of hypertension. The first such study was conducted in urban north India by Chopra and Chopra, (1942). Following this, many studies in urban and rural areas of India were carried out. Subsequent studies have shown a steadily increasing trend of hypertension in India (Gupta, 2004).

Prabhakaran et al., (2005) found prevalence of hypertension to be 30% and pre-hypertension to be 44% in the Delhi industrial population, while Mohan et al., (2007) recorded hypertension prevalence at 36.1% in the Chennai urban population. Very few studies have looked at the prevalence of pre-hypertension in India. The pre-hypertension prevalence rate is high among the affluent urban Indians.

In the last three decades, heart disease rates in urban India, particularly in south India, have risen by more than three times, from 3% to 11%. The state of Kerala has a prevalence of 13% in urban areas and 7% in rural areas (Prasanth et al., 2008). Predictors of hypertension may be different in different geographical regions of South India & East India (Sharma, 2006).

Effective screening strategies, therapeutic interventions, educational programs, and other preventive measures are urgently needed to reduce the alarming increase in the prevalence of hypertension in India. Right drug in right dose for right person is what pharmacology is trying since time immemorial. Pharmacoepidemiology is the best method to quantify drug exposure and evaluate the effectiveness and safety of drug treatment in the general population (Leufkens and Urquhart, 1994; Storm, 2000).

Despite a variety of effective antihypertensive drugs and available guidelines (JNC-8), the control of blood pressure is inadequate and is responsible for a large proportion of cardiovascular diseases in the population (Schelleman et al., 2004). Developments in antihypertensive therapy have been associated with marked reduction
in morbidity and mortality from hypertension. But the effectiveness of treatment is hampered by the problem of non-compliance with ingestion of drugs and the trial-and-error approach (Amal et al., 2009). Although the trial-and-error approach can be efficient in treating high blood pressure, it is not appropriate with regard to long term effects such as stroke.

Many drugs have proven to be effective in treating hypertension, but an individual patient’s response to these drugs is unpredictable. Today there are no effective methods with which to individualize antihypertensive treatment. This is the essence of the question addressed in this thesis: How do we know which drug to choose for which hypertensive patient?

Humans share around 99.9% of their genome and very little variation (0.1%) exists in the form of approximately three million polymorphisms, the most common being the single nucleotide polymorphisms (SNP). A gene is considered polymorphic when its allelic variant(s) exist in a population with a frequency of at least 1%. Many of these polymorphisms in the human genome will have no effect. Some, however, will affect protein expression or function, resulting in phenotypes affected by disease or with altered drug response (Meyer, 1990). Pharmacogenomics focuses on the interplay between polymorphism in genes and variable response to drugs or their adverse effects. The fact that genes play a role in responsiveness to drug therapy is now known for nearly half a century and gave birth to Pharmacogenomics. It is a well known fact that systematic discovery of genetic variation will allow better diagnostic and therapeutic modalities (Bansal et al., 2005).

The field of pharmacogenomics is focused on providing an understanding of the genetic contribution to variable drug response. Pharmacogenomics is one of the most promising disciplines for the pharmaceutical industry to emerge in the post-genomic era. Pharmacogenomics can be defined as the study of the impact of genetic variation on the efficacy and toxicity of drugs or the study of how genetic makeup determines the response to a therapeutic intervention (Alwi, 2005).
Over the years, it has become clear that essential hypertension is not a Mendelian single gene disorder but rather a complex trait resulting from the interaction of several environmental and genetic factors. But there is an inherent contradiction. Despite the widely recognized fact that primary hypertension is very heterogeneous in terms of pathophysiological mechanism, organ complications, and response to therapy, many researchers have tried to find factors contributing to variation in BP levels within and between populations. Environmental factors play a significant role in the observed variations in the distribution of BP among different population groups (Borhani et al., 1969). Socio-cultural differences, rather than genetic heritability, have been found to be responsible for the majority of the differences in BP levels between populations (Ward, 1983). Age and sex differences are well known. Despite extensive preclinical and clinical investigations, the molecular mechanism of the normal regulation of arterial pressure and development of essential or primary hypertension are far from clear. Therefore, determination of the relative roles of genes and environment in the etiology of high BP is very important.

Only a few studies have focused on evaluating individual response to antihypertensive drugs. Diversity in responses to antihypertensive therapy is well documented. African & Americans are reported to be more responsive to diuretics and calcium channel blockers and less responsive to β-blockers and angiotensin converting enzyme inhibitors than their Caucasian counterparts (Hall, 1987; Jamerson, 1996; Materson, 1993; Seedat, 1989 and Weder, 1994). However, it is not yet known why they respond differently and how to select a therapy in individual patients within the same ethnic group.

Based on the clinical trials designed to compare the efficacy of two antihypertensive drugs, the question we asked was: Can we relate the individual patient’s drug response to his/her genotype?

Variation in drug response in a disease is attributed to many genes rather than a single gene mutation. Therefore, instead of taking into account single gene mutations, it would be appropriate to do pharmacogenomics study comparing single nucleotide polymorphism (SNP) maps and gene expression between normal and affected
individuals. This can identify the genetic factors associated with the disease and thus provide newer targets to characterize and evaluate for the purpose of drug development. The potential future drug targets can be called tractable or drugable targets (McCarthy et al., 2005). With the availability of advanced human genome sequences, the genes can now be analyzed in silico for coding regions of the tractable targets. Selection of the right target for development of a drug is vital, and pharmacogenomics can play a vital role in it.

Studies that have approached the problem of a possible association between treatments and the angiotensin-converting enzyme/angiotensinogen genetic variants have produced contradictory results. Dudley et al., (1996) investigated whether the M235T polymorphism of the angiotensinogen (AGT) gene and the insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene could be used to predict blood pressure in response to β-blockers, ACE inhibitors or calcium antagonists in essential hypertensive patients. They recorded a large variability in the individual responses of blood pressure to these agents. However, this variability could not be associated with the considered polymorphisms. In another study, Hingorani et al., (1995) found an association between the M235T angiotensinogen genetic variants and the magnitude of the decrease in blood pressure after ACE inhibition.

Another example would be the variation in drug response to ACE inhibitors (Kohno et al., 1999). Different studies have shown different association between the genotypes ACE I/I, ACE I/D and ACE D/D and response to ACE inhibitors. Hernandez et al., (2000) have shown a significant reduction in the left ventricular mass index in renal transplant patients with LVH on treatment with lisinopril with ACE D/D genotype. Kohno et al., (1999) showed that patients with ACE D/D genotype are less likely to have regression of LVH, when treated with ACE inhibitors. Thus, a broader study involving multiple genes or allele variants is needed to understand the intricacies of drug response variability and to identify the factors affecting it.

There is a correlation between polymorphism and antihypertensive therapy. Antihypertensive drugs lower blood pressure by acting on specific targets. Since many components of the body system are proteins that may vary in structure, configuration, or
level because of genetic differences among individuals, it is reasonable to expect that
variation in blood pressure responses to these drugs would in part be genetically
determined.

Polymorphisms of these genes could be responsible for large interindividual
differences in the metabolism of several antihypertensive agents. Many of the
polymorphisms investigated in pharmacogenetics studies were already associated with
blood pressure regulation in population-based association or link age studies.

Based on the abundance of single nucleotide polymorphism (SNPs) in the
human genome, it is reported that one or more SNPs occur in each of the genes
encoding for the mentioned players involved in regulating blood pressure, e.g. the
insertion and deletion (I/D) polymorphism of ACE gene allows individuals to make
different amounts of this enzyme which produces angiotensin II and degradation of
bradykinins which could lead to hypertension; β1-adrenoreceptor having Ser49Gly
polymorphism stimulates the sympathetic nervous system following depolarization and
can lead to hypertension. Similarly, α-adducin (ADD1) gene with Trp460Gly
polymorphism is associated with salt sensitivity and the Trp alleles of this gene have an
increased risk of hypertension due to enhanced renal tubular sodium reabsorption
(Stakos et al., 2002).

Very little information is available on the role of candidate gene polymorphisms
in the etiology of essential hypertension or variability in drug response among patients
from North India. Till date, no pharmacogenomic study has been undertaken in Haryana
for antihypertensive drug therapy. This study was undertaken to fill this void. Hence,
the main the objectives of this study are:

1. To find out the prevalence of essential hypertension, in a rural population of
Haryana, in a hospital based study.

2. To compare the anthropometric parameters between essential hypertensive and
normotensives subjects to ascertain the risk factors involved in causing essential
hypertension.
3. To assess the current prescribing pattern of antihypertensive therapy among the patients and its outcomes.

4. To analyze the role of candidate gene polymorphisms of Angiotensin-Converting Enzyme (ACE), Ú-adducin (ADD1) and ß1-adrenoreceptor (ß-1 ADR) genes in the etiology of hypertension.

5. To correlate the polymorphism of candidate genes with control of blood pressure in essential hypertensive patients treated with different class of anti-hypertensive drugs.