Hypertension is a major contributor to diabetes, with both dependent and non-dependent complications. Most commonly, 60% of diabetic patients are hypertensive, and between 50% and 70% of hypertensive patients are diabetic (Stern et al. 1993). Over 80% of diabetics are considered to be hypertensive (Kothiwala et al. 1990). They are at significantly increased risk of developing certain cardiovascular complications, such as myocardial infarction, stroke, and diabetic nephropathy (Kothiwala et al. 1990). In addition, the renin-angiotensin-aldosterone system (RAAS) is known to be dysregulated in diabetes, particularly in type 2 diabetes (Yudkin et al. 1991). This dysregulation is thought to contribute to the development of hypertension. The importance of controlling blood pressure in diabetes has been emphasized by several studies (Feldman et al. 1986, Madias et al. 1994). The relationship between high blood pressure and diabetes is well-established, with diabetes being a major risk factor for hypertension. Patients with diabetes are at an increased risk of developing hypertension, which is often refractory to treatment. This is a significant concern, as hypertension is a major contributor to cardiovascular disease (CVD). Therefore, lowering blood pressure in diabetes is crucial for managing CVD risk.
Hypertension is more common in persons with insulin dependent and non-insulin dependent diabetes mellitus. Approximately 80% of diabetic patients are hypertensive and between 5-25% of hypertensive individuals are diabetic (Stamler et al 1993). Over 80% of diabetic patients are non-insulin dependent (NIDDM or type II). They are usually obese and tend to have a typical metabolic derangement including hyperinsulinemia, the characteristic dyslipidemia of a low high density lipoprotein (HDL) cholesterol and elevated triglycerides (Reaven 1988). In addition to the increased risk of atherosclerosis, these patients develop microvascular complications such as nephropathy (Rosenstock and Raskin 1986) and retinopathy (Knowler et al 1980). It is also likely that glucose intolerance exacerbates the cardiovascular risk factors associated with hypertension in the diabetic patients (Kannel 1985). Like diabetes-mellitus long standing hypertension commonly leads to target organ diseases, such as congestive cardiac failure, coronary heart disease (Castelli 1984, MacMohan et al 1990), renal impairment (Zatz et al 1986), and cerebrovascular damage (Kuller et al 1985, Palumbo et al 1978). Metabolic abnormalities, such as dyslipoproteinemia and impaired glucose tolerance are commonly found in hypertensive patients and the metabolic abnormalities may be found even in patients of normal weight (Fuh et al. 1987). There are several reports suggesting that hypokalemia impairs insulin release. Patients with primary and secondary hyperaldosteronism showed impaired carbohydrate metabolism (Conn, 1965) and this has been attributed to aldosterone-induced hypokalemia, which interferes with the insulin secretory response to glucose, thereby, worsening glucose tolerance (Gordon, 1973). Thus, while both diabetes and hypertension appear to be strong independent risk factors for coronary heart disease (CHD) and stroke, risks are greatly enhanced when these two risk factors coexist (Kannel 1985, Kannel 1978).

Further, it has been reported that the combination of elevated blood pressure, glucose intolerance, obesity, low HDL cholesterol, and elevated serum triglycerides 'cluster' in diabetic patients (Reaven 1988; Fuh et al 1987). A concept that has emerged linking diabetes mellitus and hypertension is the existence of hyperinsulinemia and associated insulin resistance. Increasing epidemiological data points to a striking association of hypertension with hyperinsulinemia (insulin resistance) in diabetic subjects (Levy et al 1989; Reaven & Hoffman 1989; Modan et al 1985). Correlation between hyperinsulinemia and blood pressure has been found in obese and lean hypertensives (Landsberg and Krieger 1989; Ferrannini et al 1987). Welbom et al (1966) reported that
plasma insulin levels were elevated in patients with essential hypertension when compared to normotensive controls. However, in this study differences in body weight and age were not taken into account. Berglud et al (1982) reported that untreated hypertensive patients had higher body mass index (BMI), higher fasting insulin levels and had impaired glucose tolerance. Moreover, even after correction for BMI, fasting insulin levels were found to be elevated in this study. In a large-population study including 2769 patients, Modan et al (1985) found a significant association between hypertension and plasma insulin levels after an oral glucose load that was independent of obesity, glucose intolerance under fasting conditions, and age. When compared to normotensive controls, the whole body glucose uptake of lean hypertensives during a hyperinsulinemic euglycemic clamp was found to be reduced by 30-40%. This further suggested an association between insulin resistance and pressure in non-obese subjects (Ferrannini et al 1987). There are several reports suggesting a subnormal response to insulin effect on glucose uptake in peripheral tissues leading to a compensatory hyperinsulinemia, which, in turn, causes hypertension through its effects on kidneys, sympathetic nervous system, and cardiovascular system that cause hypertension. Insulin is known to stimulate the sympathetic nervous system activity resulting in significant elevation of plasma catecholamine levels (Christensen et al 1987, Rowe et al, 1981). Secondly, sodium retaining property of insulin probably acting at the level of proximal tubule is also well documented. This results in increase in total exchangeable body sodium, as well as vascular volume. Increased total sodium is a feature of NIDDM (De Fronzo et al, 1975). Insulin is a growth factor promoting vascular smooth muscle growth in vitro thereby resulting in narrowing of lumen of resistance vessels, consequently raising vascular resistance (Cruz et al 1981). All these factors in turn contribute to the development of hypertension (Pfeifle et al, 1981). Yet another approach in understanding the link between impaired glucoregulatory actions of insulin and simultaneously occurring hypertension and diabetes is the association of insulin with the renin-angiotensin-aldosterone system (RAAS) and potassium levels.

The aim of antihypertensive treatment is to lower elevated blood pressure as a means to reduce or prevent the cardiovascular and metabolic complications of hypertensive patients. However, hypertensive patients differ among themselves for many characteristics such as age, sex, organ damage, metabolic pattern, concomitant disease, etc. Furthermore, antihypertensive treatment is symptomatic, and may not remove the
cause or causes of blood pressure elevation. It produces haemodynamic changes, such as decrease in peripheral resistance or in cardiac output, in order to lower blood pressure. Claims for superiority of one drug of a group over another of the same group tend to focus on the onset, peak effect and duration of action. Over recent years "stepped care" with diuretic followed by beta-blocker or vice versa has given way to the "individualized care" considering the associated risk factors and concomitant microvascular and macrovascular disease in individual patients. This has become all the more important because large scale control trials have confirmed that blood pressure reduction reduces the incidence of stroke but has disappointingly little or no influence on CHD, which remains a major cause of hypertensive mortality in hypertensive patients (Medical Research Council Working Party 1985; International prospective primary prevention Study in Hypertension Collaborative Group 1985; Wilhelmsen et al 1987). When treating hypertension in patients with diabetes mellitus, metabolic effects of antihypertensives require special consideration as some antihypertensive agents may produce undesirable metabolic effects in the long term treatment.

A plethora of drugs are available for antihypertensive therapy. Among themselves they have several advantages and disadvantages. Our laboratory has been engaged for over a decade in investigating the effects of antihypertensive agents on cardiovascular and metabolic complications in STZ-diabetic rats and also diabetic hypertensive patients. It was found that while all antihypertensive agents under study effectively lower blood pressure in STZ-diabetic rats, and also in diabetic hypertensive patients, there were differences with respect to the effectiveness of different classes of drugs on cardiovascular, metabolic and functional alterations induced by diabetes and/or hypertension. Cardioselective beta,-adrenoceptor blocker atenolol was not found to improve diabetes-mellitus induced cardiac dysfunctions, cardiomyopathy and metabolic disturbances like insulin resistance and hyperlipidemia (Bangaru et al 1996). In fact, atenolol was found to cause a depression in cardiac function in STZ-diabetic rats. Clinical trials in our laboratory have shown that atenolol does not improve glycemic control in diabetic hypertensive patients (Satia et al 1995). It has been reported that beta,-adrenoceptor blockade in hypertensive NIDDM patients can prolong hypoglycemetic episodes by blocking glycogenolysis in muscle and lipolysis in adipose tissue, thereby reducing the substrates for both gluconeogenesis and ketogenesis (Christlieb and Maki 1980). Secretion of glucagon, that is mediated through beta,-adrenoceptors and is needed
in hypoglycemic episodes, is also hampered by beta₂-adrenoceptor blockade. Beta₂-adrenoceptor blockade may provoke hypertensive crisis during hypoglycemia, as overstimulated alpha receptor dominated arteriolar constriction is no longer counterbalanced by beta₂-adrenoceptor mediated arteriolar dilation (Christlieb and Maki 1980). Further, non-selective beta-adrenoceptor blockers impair the perception of symptoms of hypoglycemia.

Vasodilator hydralazine was found to improve cardiac performance, cardiomyopathy and also prevent hyperlipidemia in STZ-diabetic rats (Rodrigues et al 1986). Hydralazine has been reported to lower blood lipids in hypertensive patients (Deming et al 1958). Prazosin, a vasodilator with alpha adrenoceptor blocking activity has been shown to increase plasma glucose levels in diabetic patients (Barbieri et al 1980). However, another group of workers have reported that chronic treatment with prazosin (3 mg/Kg) improves glucose tolerance with small increase in insulin levels in diabetic patients (Barbieri et al 1981). Data from our laboratory suggests that prazosin does not alter hyperglycemia in STZ-diabetic rats (Goyal et al 1996). Chronic prazosin treatment, however, prevents cardiac depression and cardiomyopathy in STZ-diabetic rats (Goyal et al 1996).

Guigliano et al (1980) have shown that nifedipine is potentially diabetogenic when administered for less than a month to subjects with/without cardiovascular disease and with normal or reduced glucose tolerance. Chellingsworth et al (1989) reported that fasting plasma glucose levels were increased in hypertensive and NIDDM patients treated with nifedipine for 4-6 weeks. On the other hand, many single-dose studies have shown that nifedipine has no significant effect on glucose tolerance in healthy volunteers and in subjects with impaired glucose tolerance or diabetes-mellitus (Abadic and Pass 1984, Anderson et al 1982, Brauman et al 1984). Several other clinical trials do not show any clinically important effect on glucose homeostasis when calcium antagonists are used in therapeutic doses (Collins et al 1987, Faguer Moustier and Paoli 1990, Hedner et al 1987, Kihara 1991, Marre and Fressiraud 1990, Tebtorio et al 1989, Pasansri et al 1989). Studies with laclidipine by Morris et al (1993) and diltiazem by Poliare et al (1989b) showed that these calcium antagonists do not influence insulin sensitivity in human subjects. It is apparent that reports with respect to effects of calcium antagonists on carbohydrate metabolism and insulin sensitivity are controversial. Data concerning the
influence of calcium antagonists on lipid profile are also conflicting (Vessby et al. 1983, Ohman et al. 1985, Satia et al. 1995, Houston et al. 1990). Investigations into the effects of calcium antagonists in our laboratory revealed that most of the antihypertensives belonging to these classes improve cardiac functions, cardiomyopathy (Shah et al. 1995, Joshi et al. 1996), lipid profile and carbohydrate metabolism in STZ-diabetic rats. These agents were also found to have neutral effects on liver and kidney functions in STZ-diabetic rats (Shah et al. 1995). Calcium antagonist, nitrendipine, partially prevented depression of cardiac function (Joshi et al. 1996). A reduction in insulin output with nicardipine was observed by Marre and Fressinaud (1990) in isolated perfused pancreas. In our laboratory we found that nifedipine produces lowering of blood glucose levels despite decrease in serum insulin levels suggesting that nifedipine probably increases insulin sensitivity in STZ-diabetic rats (Shah et al. 1995). Nifedipine was also found to prevent cardiomyopathy and hyperlipidemia in STZ-diabetic rats (Shah et al. 1995). In clinical studies it was reported that in diabetic hypertensive patients treated with nifedipine the dose of oral hypoglycemic agents had to be reduced (Satia 1995).

ACE inhibitors have been reported to produce a reduction in insulin requirement or discontinuation of oral hypoglycemic therapy after the introduction of either captopril or enalapril (Ferriere et al. 1985, Mc Murray et al. 1986) even hypoglycaemic episodes were attributed to ACE inhibition (Rett et al. 1988). Investigations in our laboratory with enalapril (Goyal et al. 1997), lisinopril (Sevak and Goyal 1996) and perindopril (Reddy 1996) suggest that these agents prevent diabetes-induced cardiomyopathy, cardiac dysfunctions, hypercholesterolemia and glucose levels in Wistar rats. Clinical studies with ACE inhibitor enalapril on glucose metabolism have shown that in diabetic hypertensive patients a reduction in the dose of oral hypoglycemic agents becomes necessary (Satia 1995).

From the above mentioned discussion it can be stated that among various groups of antihypertensives the calcium antagonists and ACE-inhibitors are comparatively a better choice for hypertension when it is associated with diabetes-mellitus.

STZ-induced diabetic rat model has long been used for investigation of the effect of various classes of antihypertensive drugs on diabetes-induced cardiovascular and metabolic complications. STZ-induced hypertension is a well established form of
experimental hypertension since its demonstration in Sprague-Dawley rats by Kawishima (1978). Other workers also reported that STZ not only induces diabetes but also hypertension in rats (Hayashi et al 1983, Funakawa et al 1983). Alterations of the prostaglandin and/or the kallikrein-kinin systems, impaired renal prostaglandin E2 synthesis, and altered hypothalamic pressor responses have been suggested to play a role in the development of hypertension in STZ-induced diabetic rats (Hayashi et al 1983, Funakawa et al 1983). However, there are other reports that do not support the existence of hypertension in STZ-diabetic rats (Kohler et al 1980, Pfaffman 1980). Rodgers et al (1985) reported that STZ induces a depressor effect in spontaneously hypertensive (SH) rats and does not produce any effect in Wistar Kyoto rats. Somani et al (1979) and Kusaka et al (1987) reported that STZ induces a dose-dependent decrease in blood pressure in SH rats. Blood pressure measurements in most of the studies were done by indirect tail-cuff method. It has been suggested that the mechanism by which STZ treatment induces depressor effects in Wistar Kyoto and SH rats may be associated with a reduction in vascular collagen biosynthesis (Rodgers et al 1985), plasma vasoactive factors (Funakawa et al 1983), or vascular reactivity to plasma vasoactive factors (Takiguchi et al 1987). Kusaka et al (1987) further suggested that emaciation of the tail in diabetic rats results in structural changes that possibly lead to extra pressure requirement above the maximum to occlude the tail artery.

Thus, there is a controversy as to the development of hypertension after STZ treatment is concerned. In the light of this controversy work was carried out with STZ-diabetic DOCA-hypertensive rats. Hebden et al (1990) have reported that this model may be a useful one as it resembles the clinical conditions in humans where diabetes mellitus, hypertension and atherosclerosis occur simultaneously. It was found that DOCA treatment in STZ-diabetic rats did not result in development of severe hypertension (Sevak and Goyal 1996). Moreover, the cardiac depression and cardiomyopathy observed in STZ treated animals was found to be prevented when these animals were treated with DOCA (Sevak and Goyal 1996). Similar findings have been reported by other workers (Dai and McNeill 1992). It was found that STZ-diabetic DOCA-hypertensive rats had lower insulin levels when compared to nondiabetic DOCA-hypertensive rats and milder hyperglycemia when compared to STZ-diabetic rats. This suggested that DOCA may have some influence on glucose homeostasis and insulin sensitivity (Sevak and Goyal 1996). It
appears that a sort of counteraction to diabetes induced cardiovascular and metabolic changes occurs with DOCA (Sevak and Goyal 1996, Dai and McNeill 1992).

Spontaneously hypertensive (SH) rats are genetically predisposed to hypertension. Several studies on anesthetized SH rats have indicated that they are insulin resistant and have high circulating levels of insulin (Hulman et al 1991, Mondon and Reaven 1988). It has been proposed that defect in insulin action in SH rats is distal to the insulin receptor (Reaven et al 1989a). Although hyperinsulinemia in SH rats has been confirmed by several studies (Buchanan et al 1992a, Frontoni et al 1992, Bhanot et al 1994), existence of insulin resistance in this rat model of hypertension is still controversial (Buchanan et al 1992b, Frontoni et al 1992). The hyperinsulinemic hypertensive SH rat appeared to be a good model for the present study.

Neonatal administration of STZ produces a condition of NIDDM in later life (Wier and Clore 1981). In our laboratory it was found that neonatal STZ administration produces hyperglycemia, hyperinsulinemia and hypertension at 16 weeks of age. This model of NIDDM proved to be useful for the present study.

In the light of the above discussion the present investigation was carried out to evaluate suitability of different animal models for the study of cardiovascular and metabolic complications of diabetes-mellitus and hypertension. Further, we also studied the effects of newer calcium antagonists amlodipine and nifedipine and ACE inhibitors spirapril and ramipril on cardiovascular and metabolic alterations in different rat models of diabetes and/or hypertension.