2. LITERATURE REVIEW

1. Calò et al., (1998) were studied that the antihypertensive and metabolic effects of doxazosin in hypertensive patients with type 1 diabetes. Author shown that the drug normalizes blood pressure, and while no improvement in glucose control was observed, it reduced total cholesterol and increased HDL cholesterol as well as the HDL to total cholesterol ratio. The changes of the various parameters studied, including the calculated CHD risk score based on the Framingham equation, suggest that doxazosine can reduce the CHD risk for hypertension type 1 patients.

2. Shougo Kaneko et al., (1999) investigated the renal protective effect of nifedipine (2-nitrophenyl derivative BAY a 1040) in streptozotocin (STZ) - induced spontaneously hypertensive rats (SHRs, 8 weeks of age). Author suggested that nifedipine inhibits the development of albuminuria and glomerular enlargement in STZ-induced diabetic SHRs. There was no significant difference in the changes in antihypertensive or antialbuminuric effects between nifedipine and efonidipine. Thus, nifedipine, as well as efonidipine, may become a useful antihypertensive drug with a renal protective effect.

3. Masahiro Takeda et al., (1998) investigated the renal protective effect of efonidipine hydrochloride (efonidipine, NZ-105) in STZ-induced spontaneously hypertensive rats (SHRs, 8 weeks of age). Author suggested that efonidipine inhibits the development of albuminuria and glomerular enlargement in the streptozotocin-induced diabetic SHRs and may become a useful antihypertensive drug with a renal protective effect.

4. Huang et al., (2006) were studied that the effect of carvedilol on the antioxidant status in diabetic hearts. Author investigated carvedilol - administrated healthy and streptozotocin-induced diabetic rats. Carvedilol treatment increased activities of antioxidant enzymes and expression of Bcl-2 in healthy rats as well as diabetic rats. These results indicated that carvedilol partly improves cardiac function via its antioxidant properties in diabetic rats.

5. George L. Bakris, et al., (2001) were studied that comparision of the effects of beta -blockers with different pharmacological profiles on glycemic and metabolic control in participants with DM and hypertension receiving rennin
angiotensin system (RAS) blockade, in the context of cardiovascular risk factors. A randomized, double-blind, parallel-group trial (The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives [GEMINI]) conducted between June 1, 2001, and April 6, 2004, at 205 US sites that compared the effects of carvedilol and metoprolol tartrate on glycemic control. Both beta-blockers were well tolerated; use of carvedilol in the presence of RAS blockade did not affect glycemic control and improved some components of the metabolic syndrome relative to metoprolol in participants with DM and hypertension. The effects of the 2 beta-blockers on clinical outcomes need to be compared in long term clinical trials.

6. **Ebbehøj et al., (2004)** this study is the first to address the QTc interval and QTc dispersion in Type 1 diabetic patients treated with metoprolol. Beta blocker treatment caused a decrease in QTc interval but no change in QTc dispersion. These results may in part explain the pronounced cardioprotective effect of beta blocker treatment in diabetic patients with cardiovascular disease.

7. **Carl J. Pepine et al., (2004)** reported that the prevalence of diabetes is increasing, and patients with diabetes are at increased risk of adverse cardiovascular outcomes. Recently, the results from 11 large randomized clinical trials have suggested a difference in the emergence of new diabetes according to cardiovascular medication use. Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium antagonists yielded a lower incidence of diabetes development than beta blockers and diuretics. Physicians should consider this possible diabetes consequence when prescribing long-term beta-blockers and diuretics, particularly in patients at high risk of developing diabetes.

8. **Adriana Georgescu et al., (2005)** examined the cellular mechanisms by which the drug induces renal artery vasodilation, an issue of potential relevance for condition associated with high blood pressure. To this purpose, myograph and patch-clamp techniques were used. The results showed that the cellular mechanisms of the vasodilator effect of nebivolol on the renal artery entail (i) activation of the endothelial h2-adrenoceptor, (ii) participation of [Ca2+]i, (iii) increase in NO and eNOS, and (iv) activation of Ca2+-activated
K+ channels. The cellular mechanisms underlying vasodilator effect of nebivolol on the artery explain the favorable effect of this drug in hypertension.

9. Istvan Edes et al., (2005) examined the effect of the beta1-selective beta-blocker nebivolol, administered as add-on therapy, on left ventricular function in 260 elderly patients (N65 years) with chronic heart failure (CHF). The principal inclusion criteria were (1) NYHA class II–IV CHF and (2) a left ventricular ejection fraction (LVEF) \( V35\% \). The primary end-point was the change in LVEF in response to nebivolol treatment for 8 months. The findings of the ENECA study confirmed that nebivolol significantly improved cardiac function and proved to be safe and well tolerated in elderly patients with signs of CHF and an impaired LVEF.

10. Matthias Oelze et al., (2006) studied the effect of nebivolol on endothelial function and NADPH oxidase activity and expression in the well characterized model of angiotensin II–induced hypertension. Angiotensin II infusion (1 mg/kg per day for 7 days) caused endothelial dysfunction in male Wistar rats and increased vascular superoxide as detected by lucigenin-derived chemiluminescence, as well as dihydroethidine staining. Vascular NADPH oxidase activity, as well as expression at the mRNA and protein level, were markedly upregulated, as well as NOS III uncoupled, as evidenced by NO synthase III inhibitor experiments and dihydroethidine staining and by markedly decreased hemoglobin NO concentrations. These findings indicate that nebivolol interferes with the assembly of NADPH oxidase. Thus, inhibitory effects of this beta-blocker on vascular NADPH oxidase may explain, at least in part, its beneficial effect on endothelial function in angiotensin II–induced hypertension.

11. Zahid Dhakam et al., (2008) reported that nebivolol and atenolol have similar effects on brachial blood pressure and aortic stiffness. However, nebivolol reduces aortic pulse pressure more than atenolol, which may be related to a less pronounced rise in AIx and bradycardia.

12. Sarah e. Capes et al., (2000) reported that clinical proteinuria is a risk factor for both end-stage renal disease and cardiovascular disease. The prevalence of clinical proteinuria, its correlates and predictive value, and the effect of ACE inhibitors in preventing clinical proteinuria in diabetic and nondiabetic
patients with left ventricular (LV) dysfunction are unknown. Clinical proteinuria is an independent predictor of hospitalization for CHF and mortality in diabetic and nondiabetic patients with LV dysfunction. Enalapril significantly reduces the risk of clinical proteinuria in diabetic patients with LV dysfunction.

13. Elena M.V. et al., (2001) studied that effect of enalapril treatment on oxidative stress and tissue injury was studied in hearts, kidneys, and livers from streptozotocin-induced diabetic rats. Enalapril treatment attenuated the oxidation of lipids in the heart and kidney \((P < 0.05)\). Tissue fibrosis scores were inversely correlated with (1) both total glutathione and reduced/oxidized glutathione in heart, kidney, and liver and (2) glutathione reductase activity in the kidney. These results suggest that in streptozotocin-induced diabetic rats, the protective action of enalapril might be mediated, at least in part, by its effect on tissue oxidant/antioxidant status.

14. Emmanuelle Vermes et al., (2002) studied that the effect of angiotensin-converting enzyme (ACE) inhibitors on the prevention of diabetes in patients with left ventricular dysfunction is unknown. The aim of this retrospective study was to assess the effect of the ACE inhibitor enalapril on the incidence of diabetes in the group of patients from the Montreal Heart Institute enrolled in the Studies of Left Ventricular Dysfunction (SOLVD). Enalapril significantly reduces the incidence of diabetes in patients with left ventricular dysfunction, especially those with impaired FPG.

15. Anna K. Trauernicht et al., (2003) were studied that effects of chronic treatment with enalapril on cerebrovascular dysfunction and endothelial nitric oxide synthase (eNOS) protein in diabetic rats. These results suggested that enalapril prevents cerebrovascular dysfunction in diabetic rats. Author conclude that the protective role of enalapril may be independent of an alteration in eNOS protein in cerebral microvessels.

16. Marco pahor et al., (2000) were studied that ACE inhibitors may provide a special advantage in addition to blood pressure control. The question of whether atenolol is equivalent to captopril remains open. Conclusive evidence on the comparative effects of antihypertensive treatments will come from large prospective randomized trials.
17. **Paul M.L. Janssen et al., (1999)** investigated the impact of hydroxyl radical on free radical induced injury in right ventricular rabbit cardiac trabeculae. Additionally, author investigated the protective properties of the beta-adrenoceptor antagonist nebivolol. The contractile response to a brief, 2 min exposure to hydroxyl radical consisted of a severe but transient rigor-like contracture, followed by a new steady state in which diastolic force remained increased and developed force remained decreased. Results indicate that hydroxyl radical injury induces systolic and diastolic dysfunction, and that nebivolol can effectively prevent a large part of this hydroxyl radical injury.

18. **Chen, J., Y. Gu, et al. (2002)** were studied that Bosentan combined with amlodipine can offer similar renoprotective effects on that of cilazapril and may be a potent therapy to attenuate renal injury by reducing renal protein levels of TGF-beta1 in diabetes with a hypertensive state.

19. **Shigihara, T. et al. (2000)** this study showed that in hypertensive microalbuminuric type II diabetic patients, the combination of an ACE inhibitor plus amlodipine resulted in a more pronounced decreased in blood pressure (diastolic blood pressure <80 mmHg) and a greater reduction in urinary albumin excretion than did use of an ACE inhibitor alone. This combination strategy should thus be a more effective tool for obtaining optimal blood pressure control in patients with diabetic nephropathy.

20. **Winer, N., A. Folker, et al. (2005)** studied that ACE inhibitors and calcium channel blockers treatments were similarly effective in lowering BP, reducing systemic vascular resistance, and decreasing urinary microalbumin excretion. Improvement in large-vessel compliance was significantly greater among subjects who received ACE-inhibitor/calcium channel blocker combination therapy (52%) as compared with those who received ACE-inhibitor monotherapy (32%; p < 0.05). No significant change in small-vessel compliance was observed with either treatment. Greater improvement in large-vessel compliance with combination therapy was independent of BP lowering.

21. **Derosa, G., A. F. Cicero, et al. (2004)** reported that in selected sample of patients with type 2 diabetes and mild hypertension, both telmisartan and nifedipine gastrointestinal therapeutic system (GITS) produced significant reductions in blood pressure. Telmisartan was associated with a slight but
statistically significant improvement in plasma TC and LDL-C concentrations compared with nifedipine gastrointestinal therapeutic system (GITS).

22. **ALLHAT Collaborative Research Group. (2002)** examined that whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs treatment with a diuretic. Authors reported that thiazide-type diuretics are superior in preventing one or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.

23. **Ko, chan et al., (2001)** compared the efficacy and tolerability of amlodipine and nifedipine retard in 64 Chinese Type 2 diabetic patients with hypertension author reported that both amlodipine and nifedipine retard are relatively safe and useful in the treatment of hypertension in Chinese Type 2 diabetic patients. Nifedipine retard, when compared to amlodipine, showed significantly more adverse effects and these may hamper long-term compliance.

24. **Mahmoudian, et al. (1996)** were investigated diabetes-induced changes in the calcium influx and contractile responses of aortic rings to various drugs in streptozotocin-treated rats. Author concluded that diabetes reduces the sensitivity of aortic tissue to nifedipine and may affect the stimulation-contraction coupling of vascular smooth muscle in such a way that a higher influx of calcium results after stimulation and that this may be responsible for diabetes-induced vascular complications.

25. **Mancia G et al. (2003) ** reported that nifedipine once daily is as effective as diuretic therapy in reducing cardiovascular complications in hypertensive diabetics. Nifedipine-treated patients were also less likely to have diabetes or have secondary events than co-amiloride recipients. Author suggested that nifedipine could be considered as first-line therapy for hypertensive diabetics.

26. **Hansson L, et al. (2000)** compared the effects of diltiazem with that of diuretics, beta-blockers, or both on cardiovascular morbidity and mortality in hypertensive patients. Author reported that diltiazem was as effective as treatment based on diuretics, beta-blockers, or both in preventing the combined primary endpoint of all stroke, myocardial infarction, and other cardiovascular death.
27. The DREAM Trial Investigators. (2006) were investigate that among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death but does significantly increase regression to normoglycemia.


29. Qu, F. Z., et al. (2009) Investigate the effects of valsartan on myocardial expression and activity of calcium/calmodulin-dependent protein kinase-II (CaMK II) in a rabbit model of heart failure. Conclude that valsartan improved cardiac function in heart failure rabbits probably via downregulating myocardial CaMK II expression and activity.

30. Erdamar, H. et al. (2009) were studied that patients with Cardiac syndrome X who taken nebivolol have lower serum MPO activity, levels of MDA and higher serum SOD activity, NOx levels when compared with metoprolol treatment. Exercise stress test parameters were also ameliorated in patients who had taken nebivolol in contrast to metoprolol. Nebivolol treatment may be a novel treatment strategy in cases with CSX in the future.

31. Kuti, E. L. et al. (2007) were reported that Calcium channel blockers may be associated with reduced odds of developing new-onset type 2 diabetes compared to diuretics and beta-blockers.