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CARVEDILOL MORE THAN MERE A BETA-BLOCKER

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ABSTRACT

Carvedilol is a cardiovascular drug of multifaceted therapeutic potential, with beta-blocker and vasodilatative activity. These actions confer to the above mentioned beta blocker some beneficial properties on several processes involving cardiovascular system. Carvedilol provides hemodynamic, ant ischemic, anti-proliferative and antiarrhytmic benefits, for its antioxidant neuro humoral and electrophysiological effects. All these actions provide the basis for usefulness of the drug in the treatment of hypertension, coronary heart disease, and congestive heart failure. In this review we report the beneficial properties of Carvedilol and we analyze the rational clinical use of this beta blocker taking special attention on recent clinical trial in heart failure where it appears evidence supporting an important, favorable effect of the drug.

KEYWORDS: Carvedilol, Hypertension, Coronary disease, Hearth failure.

INTRODUCTION

In the last ten years there has been a growing interest on the use of beta-blockers in major cardiovascular disease as coronary disease and heart failure. Beta blockade has demonstrated an improving prognosis in several randomized trials. However these studies are different for size, duration, objectives and subject recruitment; each beta-blocker has different effects on the cardiovascular system and the appropriate clinical use is not the same for all these drugs. Particular interest has been developed in these drugs around the treatment of heart failure: the failing heart is adrenergically activated and this phenomenon helps to 0aintain an adequate cardiac performance at short term but it is damaged after an early period1. This observation has encouraged several Authors to study the effect of beta-blocker in heart failure obtaining good results in morbidity and mortality. Recent critical meta analysis showed different evidences on beneficial effects and survival for various beta blocker employed.[2,3] Carvedilol is one of the most analyzed beta blockers and the only one to have shown a clear reduction in mortality; compared with other drugs of the same class it has additional advantageous properties and should be considered as part of the routine treatment of heart failure. In this article we analyze molecular biological and potential activities of the drug.

Clinical Use of Carvedilol

Hypertension

The haemo-dynamic effects of beta and Alfa blockade of the drug are well recognize and thanks to these cardiac and vascular affects Carvedilol is now considered one of the most important beta-blockers for the treatment of hypertension.[18] Potential effects of beta block on left ventricular remodeling. Reduction in heart rate, Reduction in O2 consumption, Modulation of β-receptors, Protection from catecholamine toxicity, Reduction of renin-angiotensin activity, Anti-ischemic and antiarrhytmic effect, Improvement in synthesis of myocardial proteins, Peripheral vasodilatation, Decrease of heart work, Antioxidant action, Anti-inflammatory action**.** In clinical trials, Carvedilol showed an efficacy equivalent to other common beta Adrenoreceptor antagonists, dihydropyridine Ca-antagonists, and ace-inibithors.[4,6,19,20] Reduction of blood pressure level is obtained without an impairment of systolic function and change in heart rate: in fact the beta-blocker effect is modulated to vasodilatative activity that reduces the above blockade with less slowing of cardiac frequency respect to other drugs of the same type. Respect to Metoprolol, Carvedilol demonstrated to lower blood pressure and systemic vascular resistance without reduction in cardiac output20. The mean dosage of Carvedilol in hypertension is 25 or 50 mg alone or with other antihypertensive drugs if blood pressure level is not well controlled. The most common medical associations are with angiotensin converting enzyme inhibitors, calcium antagonists and diuretics[5]

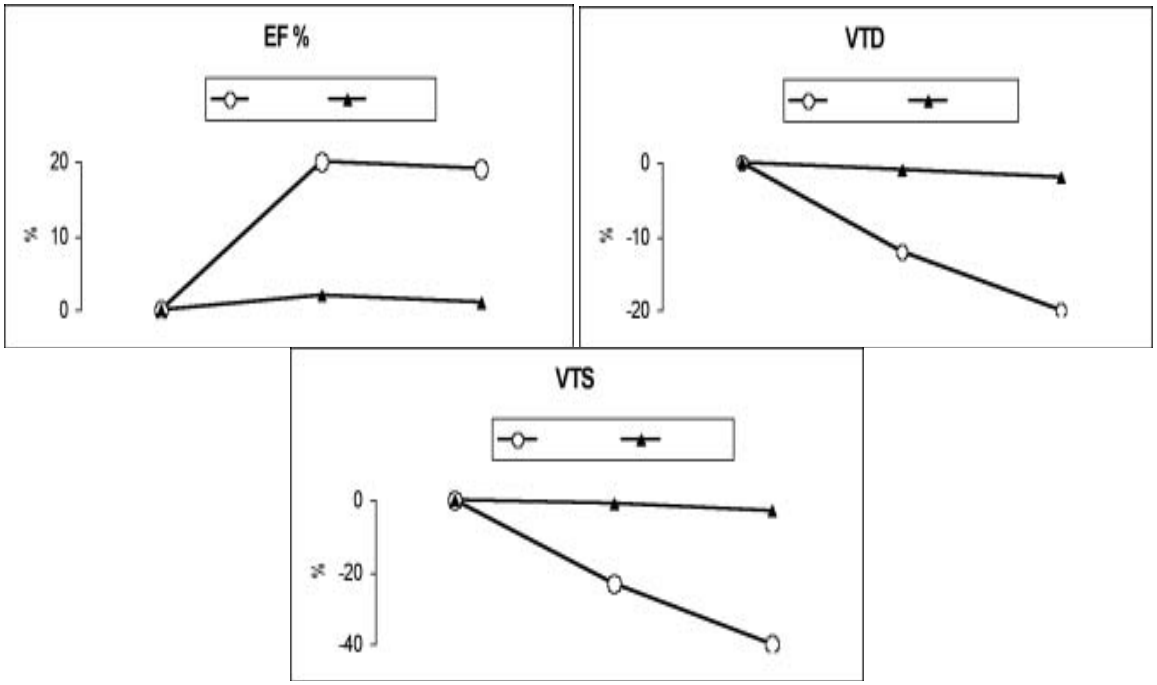
Coronary Disease

Carvedilol is useful in the treatment of stable, unstable angina and myocardial infarction. Instable angina it demonstrated to reduce ischemic attacks and to improve threshold of chest pain; in a compared study with verapamil, Carvedilol showed similar effect on symptoms and ECG alterations.[21] Respect to metaprolol

it provides a major clinical benefit in exercise tolerance with same anti ischemic and anti anginal effects. This could be due to the antioxidant and vasodilator properties that bring less adverse consequences in comparison to traditional beta-blockers5,[22] In unstable angina Carvedilol added to conventional therapy is able to reduce heart rate, blood pressure, number and duration of ischemic attacks.[23] The beneficial effects of beta-blockers during and after myocardial infarction are well recognize although Carvedilol seems to have additional benefits respect others beta-blockers: this is due to its ancillary, metabolic and cardio protective actions.[24,25] The most important effect is the reduction of infarct size area when administered during the first 24 hours also at low dosage; this benefit is not joined with a depression of ejection fraction or indices of systolic function reduction. For its properties in membrane stabilization, Carvedilol is able to reduce dangerous ventricular arrhythmias during early phases of ischemia14. Recently, a randomized trial provided a clinical evidence of its benefit in the treatment of AMI at early and long term: Carvedilol demonstrated to reduce cardiac death, reinfarction, angina and heart failure. Its use resulted in a significant reduction of left ventricular remodeling together with increase of systolic function. In addition, in patients with pump dysfunction it can be used with good tolerability and efficacy starting with low dosage and increasing after the first week. The improvement of the contractility allows a less parietal kinesis alteration and a LV enlargement reduction.[26] These observations suggest that Carvedilol is one of the most useful beta-blockers during myocardial infarction in patients with or without systolic dysfunction; it prevents other ischemic events and adverse LV remodeling that lead to heart failure.[27]

Hypertrophic Cardiomiophaty

Carvedilol seems to be able to reduce diastolic performance linked to dysfunction of myocardial releasing. This action could be due to Ca-antagonist property. Beta-blocker effect reduces oxygen myocardial consume and vigorous contractile activity, leading to a lowering in aorto-ventricular gradient.[28]



Reduction of LV volumes and improvement of EF during Carvedilol treatment.

Clinical Trials Analysis of Carvedilol

The role of beta-blockers in heart failure has been subject of debate for many years. The results of recent prospective, placebo controlled studies of the addition of beta blockers to standard therapy in patients with chronic heart failure have confirmed a significant beneficial effect on ventricular function, clinical status, morbidity and mortality. MDC (Metoprolol in Dilated Cardiomiophaty) was the firs great randomized, multicentric, prospective and placebo controlled trial on beta-blockers. The primary objective was to determine effects of metoprolol on mortality in patients with MDC, EF < 40% in a follow up of 12-18 months. The combined end point mortality-necessity of heart transplantation was lowered of 34%. There were also many clinical and instrumental significant improvements (NYHA class, quality of life, hemodynamic profile, EF, stress tolerance).[40] The most studied beta-blocker in heart failure is Carvedilol (Table II). The ANZ trial (Australian NewZeland Heart Failure Research Collaborative Group) studied patients with heart failure secondary to ischemic heart disease in I-III NYHA class with an EF < 45%. It has been demonstrated that Carvedilol is able to increase left ventricular ejection fraction, to decrease end-systolic and end-diastolic diameters, so to improve significantly ventricular

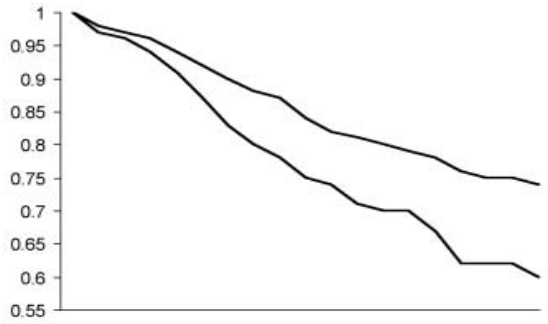
function and to maintain the exercise capacity at a lower double product.[30,41] The US Carvedilol programme trials (a cumulative analysis of 4 sub-studies) has demonstrated Carvedilol efficacy in lowering mortality, morbidity and hospitalizations in patients with mild to moderate symptomatic heart failure of various ethiology. They enrolled patients in II-IV NYHA class of various etiology- (mostly dilatative Cardiomiophaty) and with EF < 35%. The end points of these studies were the control of the progression of heart failure, the improvement in short-medium time (follow-up period of 6 months) of LV EF, the improvement in NYHA class and to find the most adequate drug dosage.

Major Carvedilol trials on heart failure

Trials	Cause of heart failure	Nyha class	Primary end point	Odds ratio	Risk Reduction
Metra	IDC	II-III	Hemodynamics	1.00	–
Olsen	IDC/CAD	II-IV	Hemodynamics	1.34	-
US Carvedilol	IDC/CAD	II-IV	Hemodynamics	–	-65%
ANZ C EF	CAD	I-III	Exercise tolerance, Morbidity+mortality	0.75	-26%
Krum	IDC/CAD	II-IV	Hemodynamic	0.70	–
Packer	IDC/CAD	II-IV	Exercise tolerance	0.39	-65%
Colucci	IDC/CAD	II-III	Morbidity+mortality	0.22	-
Cohn	IDC/CAD	II-IV	Quality of life	–	–
Copernicus	IDC/CAD	IV	Morbidity+mortality	–	-35%
Capricorn	CAD	I-II	Morbidity+mortality	–	-23%

IDC = idiopathic dilated Cardiomiophaty; CAD = coronary artery disease.

The total number of patients studied in US Carvedilol trial was lower than other trials and the mean age of patients was only 58 years. Besides the mean follow up was shorter nthan the other major beta-blocker trials, so the results of risk reduction were too favorable (in fact no patients were lost during the study for death).[42,43,44] MacDonald et al.[45] compared retrospectively the outcome of Carvedilol treatment for 3-12 months in patients with NYHA class I-III and IV. The results revealed that class IV patients are more likely to develop adverse events during initiation and dose titration compared with less symptomatic patients, yet they are more likely to show symptomatic improvements in the long term. Carvedilol improved functional classes in patients with severe heart failure who were referred for transplantation. Taken together Carvedilol may be a beneficial adjunctive therapy, even with patients with serious left ventricular dysfunction and poor NYHA classification. However, they require close observation during initiation and titration of the drug. Copernicus and Capricorn trials confirmed these data: The Copernicus Trial (Carvedilol Prospective Randomized Cumulative Survival Trial)[39] extended the use of Carvedilol also in more severe heart failure with beneficial effects on morbidity and mortality. In fact this study enrolled NYHA IV class patients in a phase of relative stability, with EF < 25% in a 10 months of follow-up period. The trial was interrupted early on a Data and Safety Monitoring Board order because the beneficial effects were greater than those expected in the end-points (Figure 3). The Capricorn Trial (Carvedilol Post- Infarct Survival Control in left ventricular dysfunction)[46], a multicentric randomized trial, was made to test the efficacy at long term of Carvedilol therapy on morbidity and mortality in patients with left ventricular dysfunction secondary to IMA. These patients were at low risk, few of them had heart failure. The primary end-point was to evaluate the mortality of every cause. The follow up was of about 15 months. All the end-points showed a favorable trend (total mortality, cardiovascular mortality, IMA, mortality due to heart failure o arrhythmias, ospedalizations).



Carvedilol has demonstrated a good efficacy also after thrombolysis for acute myocardial infarction (AMI). This efficacy has been tested in a trial from Basu et al.26, in which Carvedilol was found to be safe and it significantly reduced cardiac events in early phases of AMI, also in patients with heart failure. Such encouraging results gave the start to numerous other randomized trials regarding various problems of patients with heart failure. Among these the most important are: SPIC, Christmas, Carmen and Comet. SPIC (Italian Polycentric Study on Cardiomiophaty) values the effects of Carvedilol on quality of life, exercise tolerance, ventricular function and autonomic tone in patients with idiopathic dilated Cardiomiophaty in II-IV NYHA class and with EF < 35%. Christmas Trial (Carvedilol Hibernation Reversible Ischemic Trial; Marker of Success) is studying how the answer to Carvedilol in heart failure secondary to ischemic heart disease is

conditioned by previous myocardial conditions.[47] Carmen Trial (Carvedilol, ACE-inhibitor remodeling mild heart failure evaluation), a multicentric, randomized, double blind trial, is trying to value the effects of Carvedilol, of enalapril and of the association of both the drugs on left ventricular function and on ventricular remodeling in heart failure.[48] Comet Trial (Carvedilol or Metoprolol European Trial) is controlling the efficacy on morbidity and mortality of these two drugs in patients with heart failure secondary to ischemic and non-ischemic causes49. From various metanalyses of the trials, it has been seen an important β-blocker additive and synergetic effect in patients previously in treatment with ACE-inhibitors also on the duration or the quality of life.

Therapeutic Contraindications of Carvedilol

The main contraindications to β-blocker therapy are peripheral vascular diseases, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and asthma. Most of these side effects are due to the block of β2-receptors, while the therapeutic effects are due to the block of b1-receptors. Some favorable reduction in side effects has been obtained with further generation of β-blockers like Carvedilol. Recent data seem to show that these rules should not be applied in a rigorous way. So the introduction of Carvedilol and of the other new generation drugs have been an important step to reduce the side effects and to enlarge the therapeutic possibilities but complete safety hasn't been reached yet.

Peripheral Vascular Disease

Beta-blockers should be avoided only in those patients with vasospastic disorders, rest pain with severe peripheral vascular disease or nonhealing lesions. In patients with mild to moderate disease β-blockers can be prescribed, remaining with careful surveillance about an impairment of intermittent claudicatio. In 1991, Radak and Deck published a metanalisys in patients with mild to moderate peripheral vascular disease treated with β-blockers. The β-blockers did not worsen the peripheral disease51. It is possible that compounds like Carvedilol, thanks to vasodilator activity a1- receptors-block related, could reduce this kind of side effect.

Diabetes Mellitus

β- Blockers can reduce the peripheral sensibility to insulin and modificate in unfavorable way the LDL-HDL equilibrium I in plasma.[52-56] However, clinical trials showed that β-blocker therapy improvement in mortality and morbidity exceeded the negative influences on the glycemic and lipid risk profile.[57] In patients with heart failure, β-blockers can induce hyperglycemia, but Carvedilol, thanks to its vasodilatative activity, can improve the peripheral sensitivity to insulin for the better peripheral blood flow in themuscles. Another problem is that β-blockers can mask the metabolic answer to hypoglycemia blocking the autonomic symptoms of the neurohumoral reaction to hypoglycemia. Nevertheless, these symptoms are due to many hormones not under the autonomic control and one of the most important (sweetness) seems to depend on the parasympathetic stimulation. Therefore, β-blockers must be used carefully in diabetic patients, but not be avoided. In particular, the use of Carvedilol is contraindicated only in decompensated type II diabetes.

Chronic Obstructive Pulmonary Disease and Asthma

β- Blockers in patients with COPD and asthma must be used carefully. In asthmatic patients β-blockers-induced bronchoconstriction is conditioned by many and often impredictable variables.[58,59] So it's very difficult to identify high risk patients. Bronchial hyperactivity and reversibility of bronchoconstriction are very important elements to calculate the risk of β-blockers therapy. Particularly, non selective β-blockers are absolutely contraindicated when certain diagnosis of asthma is present, when COPD is moderate to severe (and not in mild cases), in patients on chronic bronchodilator treatment, in chronic airflow limitation with reversibility in obstruction in response to inhaled salbutamol. β-Blockers can be used when FEV1 is > 50% of the predicted value, controlling the stability of ventilatory conditions.

Bradycardia

The use of β-blockers is contraindicated when heart rate is < 50-55 bpm. Often patients are already in treatment with drugs determining heart rate reduction (digitalis, amiodarone). Often it's difficult to choose between these two types of treatment, however digitalis and amiodarone had not showed effects on mortality and survival. For this reason it seems well founded to introduce β-blockers (favoring Carvedilol) reducing or suspending other drugs determining heart rate reduction if they are not tolerated all togheter60.

Hypotension

We must be careful when hypotension is symptomatic or when systolic pressure is < 80-90 mmHg. Before contraindicating the use of β-blockers it's necessary to increase the pressure by modifying the associated therapy.[61]

Atrial Sinus Knot Diseases

β- Blockers are able to neutralize electrophysiological effects of β-adrenergic stimulation improving the slope of the 4th phase of action potential and increasing junctional conduction61. So β-blockers are contraindicated in Sick Sinus Syndrome and in II and III degree atrial sinus block because they are able to inhibit the atrial sinus automatism.

Atrio-Ventricular Block

β- Blockers have a remarkable effect on junction conduction in proportion to the power of the used β-blocker and to the single dose administered. In particular, β-blockers are contraindicated in II and III degree A-V block (in bi- and tri-fascicular blocks, also if bi-fascicular blocks are not an absolute contraindication)

because the extension of the A-V conduction time could be dangerous for the capacity to induce a marked bradiarrhythmia. Thus, patients with A-V conduction diseases and intraventricular delay must be monitored to avoid a further QRS time extension or an increase of A-V conduction time.[62,63]

Alteration of Liver Function

Carvedilol is highly lipophilic and it is metabolized in the liver and several metabolites are pharmacologically active. Its use is contraindicated when liver alterations are clinically evident,[64]

Kidney Diseases

B-blockers must be administrated carefully in renal insufficiency secondary to angiosclerosis and tubulopathy. In reno-vascular diseases β-blockers are contraindicated for their vasoconstrictive effects on the afferent arteria. However, Carvedilol has a demonstrated efficacy in patients with renal insufficiency and hypertension submitted to haemodialysis.262,63]

Cardiogenic Shock

β- Blockers effects on pressure, automatism and on the adrenergic answer make the use of this drug contraindicated in this condition. In conclusion, we can say that traditional contraindications to β-blockers can be rivalutated because the introduction of the new generation of these drugs (like Carvedilol) and the new knowledge's permit a larger use and a better prevedibility of the side effects61. Infact, clinical trials have demonstrated the importance of Carvedilol in the improvement of morbidity and mortality also in patients who were excluded in the past from this therapy because the benefits exceed eventual bad influences on risk profile.

Conclusions

β- Blockers cannot be considered as drugs with negative inotropic effects, their employment is effective in the treatment of heart failure and the chronic use has favorable actions on the LV remodeling and myocardial contractility. These actions are clear after a few months of therapy but they remain for long time. In particular, Carvedilol showed a good tolerance also in more compromised patients thanks to its vasodilator properties which allow to less bradycardia and less acute haemodynamic impairment43. Carvedilol also demonstrated minor adverse effects than other beta-blockers and it can be administered in elderly, in diabetes, in mild peripheral disease with good safety, monitoring during drugs titration clinical and laboratory conditions65. Carvedilol provides cardiovascular protection through its antiatherogenic anti ischemic and antihypertrophic actions for all ancillary molecular pro1perties its use should increase in cardiac disease leading to a clinical benefit and antagonizing adverse patophysiologic processes. The combination of all these benefits encourages its use in the treatment of hypertension, coronary heart disease and cardiac failure.

REFERENCES

1. PACKER M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol, 1992; 20:248-254.
2. HEIDENREICH PA, LEE TT, MASSIE BM. Effect of betablockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. J Am Coll Cardiol, 1997; 30: 27-34.
3. MCMURRAY JV. Major betablocker mortality trials in chronic heart failure: a critical review. Heart, 1999; 82(IV): 14-22.
4. MCTAVISH D, CAMPOLI-RICHARDS D, SORKIN EM. Carvedilol: a review of its pharmacodynamic and pharma-cokinetic properties and therapeutic efficacy. Drugs, 1993; 45: 232-258.
5. RUFFOLO RR, FEUERSTEIN GZ. Pharmacology of carvedilol: Rationale for use in hypertension, coronary heart disease, and congestive heart failure. Cardiovasc Drugs Ther, 1997; 11: 247-256.
6. DUNN CJ, LEA AP, WAGSTAFF AJ. Carvedilol. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. Drugs, 1997: 54: 161-185.
7. MORGAN T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. Clin Pharmacokinet, 1994; 26: 335-346.
8. GEHR TWB, TENERO DM, BOYLE DA, QIAN Y, SICA DA, SHUSTERMAN NH. The pharmacokinetics of carvedilol and its metabolites after single and multiple dose oral administration in patients with hypertension and renal insufficiency. Eur J Clin Pharmacol, 1999; 55: 269-277.
9. CHENG J KAMIYA K, KODAMA I. Carvedilol: Molecular and cellular basis for its multifaceted therapeutic potential. Cardiovasc Drug Rev., 19: 152-171.
10. YUE T-L, MCKENNA J, GU JL, CHENG HY, RUFFOLO RR, FEUERSTEIN GZ. Carvedilol, a new vasodilating beta- adrenoceptor blocker antihypertensive drug, protects endothelial cells from damage initiated by xanthine--xanthine oxidase and neutrophils. Cardiovasc Res., 1994; 28: 400-406.
11. FEUERSTEIN G, YUE TL, MA X, RUFFOLO RR. Novel mechanisms in the treatment of heart failure: Inhibition of oxygen radicals and apoptosis by carvedilol. Prog Cardiovasc Dis., 1998: 41(1): 17-24.
12. YUE TL, WANG X, GUE JL, RUFFOLO RR JR., FEUERSTEIN GZ. Carvedilol, a new vasodilating beta-adrenoreceptor blocker, inhibits oxidation of low density lipoproteins by vascular smooth muscle cells and prevents leukocyte adhesion to smooth muscle cells. J Pharmacol Exp Ther, 1995; 273: 1442-1449.
13. HONDEGHEM LM, SNYD`ERS DJ. Class III antiarrythmic agents have a lot of potential but a long way to go. Reduced effectiveness and dangers

of reverse use dependence. Circulation, 1990: 81: 686-690.
14. SENIOR R, MULLER-BECKMANN B, DASGUPTA P, VAN DER DOES R, LAHIRI A. Effects of carvedilol on ventricular arrhythmias. J Cardiovasc Pharmacol 1992; 19: S117-S121.
15. JACOB S, RETT K, HENRIKSEN EJ. Antihypertensive therapy and insulin sensitivity: Do we have to redefine the role of beta-blocking agents? Am J Hypertens, 1998: 11: 1258-1265.
16. SUNG C-P, ARLETH AL, OHLSTEIN EH. Carvedilol inhibits vascular smooth muscle cell proliferation. J Cardio-vasc Pharmacol, QF, 1993; 21: 221- 227.
17. OHLSTEIN EH, VICKERY L, ARLETH A, et al. Carvedilol, a novel cardiovascular agent, inhibits development of vascular and ventricular hypertrophy in spontaneously hypertensive rats. Clin Exp Hypertens, 1994; 16: 163-177.
18. MOSER M, FRISHMAN WH. Results of therapy with carvedilol a betablocker vasodilator with antioxidant propierties in hypertensive patients. Am J Hypertens 1998; 11: 15S-22S.
19. OSTERGREN J, STORSTEIN L, KARLBERG BE. Quality of life in hypertensive patients treated with either carvedilol or enalapril. Bood Press, 1996; 5: 41-49.
20. WEBER K, BOHMEKE T, VAN DER DOES R, TAYLOR SH. Hemodynamic differences between metoprolol and carvedilol in hypertensive patients. Am J Hypertens, 1998; 11: 614-617.