Carvedilol: something else than a simple betablocker?

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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 haemodynamic, anti-ischemic, antiarrhythmic and antiproliferative benefits, for its antioxidant neurohumoral 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 betablocker taking special attention on recent clinical trial in heart failure where it appears an evidence supporting an important, favourable effect of the drug.

Key Words: Carvedilol, Hypertension, Coronary disease, Heart failure.

Structure and Biological Effects of Carvedilol

Beta-blockers are able to interfere in neurohumoral modulation at various levels:

- block of the cathecolamines action and inhibition of the sympathetic activation through the block of b1 and b2 prejunctional receptors of the heart and of the surrenal marrow
- contrast receptorial alterations in heart failure (down regulation of b1 and up regulation of b2 and b3 receptors) due to high doses of norepinephrine which have negative inotropic compound (NO mediated) and a proarrhythmic effect
- restore the positive inotropic compound cyclic-AMP dependent
- decrease plasmatic endothelin (which are high in heart failure), powerful circulating vessel constrictor
increase vagal activity (increasing R-R variability and decreasing QTc dispersion, both related to arrhythmic risk)

β-receptors are divided in β₁-receptors (mostly in heart muscle) and β₂-receptors (in bronchial and vascular muscle and in many other districts such as liver, fat tissue, endocrine pancreas). No tissue contains just one type of receptors but there is a prevalence of one tie and so it's difficult to have a complete selective block of these receptors.

In recent years we have developed some compounds with particular characteristics as β₁-selectivity and intrinsic sympathicomimetic activity to obtain more effective drugs and less side effects.

Carvedilol [1-[(carbazolyl-(4)-oxy)-3-[(2-methoxyphenoxyethyl1)amino]-2-propanol] is a III generation β-blocker with a nonselective beta-adrenergoreceptor blocking effect combined with a vasodilating action based primarily on a beta₁-adrenergoreceptor blockade. It doesn't have sympathomimetic activity, but it possesses some properties called “ancillary”, such as antioxidant and antiproliferative actions.

Carvedilol is highly lipophilic and rapidly and completely absorbed after oral administration.

Oral Carvedilol undergoes extensive first-pass metabolism in the liver with a bioavailability of 20-25%. More than 95% of the drug is bound to plasma proteins. Carvedilol is primarily metabolised in the liver by cytochrome P450 enzymes and several metabolites are pharmacologically active.

The predominant way of excretion is through biliary secretion.

The pharmacokinetic profile is not altered in the elderly or in patients with renal disease. Thanks to the blockade of β₂, and α₁-adrenoreceptors Carvedilol is able to reduce blood pressure without associated reflex tachycardia.

The vasodilatory effect of Carvedilol (with lowering of total peripheral vascular resistances) is due to the blockade of α₁-adrenoreceptors.

This effect reduces afterload and offsets the negative inotropic effect of beta-block in cardiac muscle. Therefore, the stroke volume and the cardiac output are maintained or even increased.

Carvedilol do not lower renal blood flow. The antioxidant effects of Carvedilol are attributed to the presence of carbazole moiety in the drug molecule. In myocardial cell membrane Carvedilol inhibits lipid peroxidation from oxygen species of chemical and cellular origin.

Carvedilol protects smooth muscle cells (endothelial, neuronal and vascular cells) from reactive oxygen species.

Carvedilol inhibits superoxide anion (.O₂⁻) having an antioxidant activity approximately 10 times greater than vitamin E.

A better answer to reactive oxygen species damages permits a lower cardiovascular remodelig related to neutrophil activation in the inflammation.

In fact Carvedilol inhibits the attachment of the neutrophils to activated endothelial cells and vascular smooth muscle cells through a suppression of ICAM-1 gene transcription which is necessary to neutrophils to infiltrate an ischemic organ.

Carvedilol has some effects on cardiac action potential causing a moderate prolongation of action potential duration (APD) without affecting other parameters. This APD prolongation differs notably from that caused by other class III antiarrhythmic drugs in terms of frequency dependence: Carvedilol has a minimal reverse frequency-dependence and so incidences like torsades de pointes are rarer. A QT prolongation has not been observed in patients treated with Carvedilol.

Thanks to the α₁-antagonism Carvedilol is able to improve the peripheral muscle sensitivity to insulin in patients with hypertension.

Carvedilol can also inhibit proliferation of aortic vascular smooth cells induced by many types of mitogens like angiotensin II, endothelin, thrombin and growth factors, having an antihypertrophic property too (Table I).

Clinical Use of Carvedilol

Hypertension

The haemodynamic effects of beta and alpha blockade of the drug are well recognize and thanks to these cardiac and vascular effects Carvedilol is now considered one of the most important beta-blockers for the treatment of hypertension.
In clinical trials, Carvedilol showed an efficacy equivalent to other common beta adrenoreceptor antagonists, dihydropyridine Ca-antagonists, and ace-inhibitors\textsuperscript{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 output\textsuperscript{20}. 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\textsuperscript{5}.

**Coronary Disease**

Carvedilol is useful in the treatment of stable, unstable angina and myocardial infarction. In stable 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\textsuperscript{21}. Respect to Metoprolol it provides a major clinical benefit in exercise tolerance with same antiischemic and antianginal effects. This could be due to the antioxidant and vasodilated properties that bring less adverse consequences in comparison to traditional beta-blockers\textsuperscript{5,22}.

In unstable angina Carvedilol added to conventional therapy is able to reduce heart rate, blood pressure, number and duration of ischemic attacks\textsuperscript{23}.

The beneficial effects of beta-blockers during and after myocardial infarction are well recognized although Carvedilol seems to have additional benefits respect others beta-blockers: this is due to its ancillary, metabolic and cardioprotective actions\textsuperscript{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 ischemia\textsuperscript{14}. 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\textsuperscript{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 adverses LV remodeling that lead to heart failure\textsuperscript{27}.

**Hypertrophic Cardiomyopathy**

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\textsuperscript{28} (Figure 1).

**Carvedilol in Heart Failure**

Congestive heart failure is the former cause of death in the last past decade; more than 40,000 subjects died annually for this pathology and prognosis remains unaccept-
ably poor. Although introduction of angiotensin-converting enzyme has improved mortality rate, this only therapy does not appear so effective if mortality after 5 years from diagnosis is around 40%. The role of beta-blocker in heart failure has been subject of debate for many years but after recent meta-analysis results confirming the beneficial effects on mortality, morbidity and clinical status, their use is entered in clinical practice. Even if certain effects of beta-blockers may be considered class effects, it is not yet clear whether there are differences between beta1-selective antagonists and non-selective agents. Carvedilol appears to be more able than others to reduce mortality (the mortality is reduced from 7.8% to 3.2% with a rate of 65%) with highly significant effect; this seems a much larger average effect then that seen in either CIBIS or MERIT-HF. Carvedilol is the only beta-blocker approved from Food and Drug Administration for the treatment of heart failure while Bisoprolol and Metoprolol are approved for other cardiovascular indications. Improvement of symptoms and hospitalization reduction are guaranteed, functional capacity to effort does not change significantly because cardiac double product remains the same. In fact cardiac output increases but heart rate is reduced. Regarding morphological and functional aspects of left ventricle, Carvedilol reduces after a 6 months mean period LV volumes and mass, increases LV ejection fraction and fractional shortening reducing cardiac remodeling. The treatment also decreases LV mass LV sphericity causing a more elliptic morphology (Figure 2). The starting dose is low to prevent adverse and acute effects of therapy, and must be increased during the next weeks monitoring carefully blood pressure heart rate and clinical conditions. The optimized dosage is the best dose tolerated ranging from 25 to 50 mg of the drugs. Once heart failure subjects reach a maintenance dose of beta-blocker treatment, this should be maintained indefinitely because of the risk of deterioration on withdrawal.
The major actions of Carvedilol are the prevention and antagonism of cardiac adrenergic damage; heart rate lowering and reduction of oxygen consumption are two other effects of antagonism. In the failing heart strength-frequency curve shows an inverse linear correlation, so an increase of frequency is associated with a myocardial contractility reduction. The chronic use of beta-blocker is associated to an increase of ejection fraction and lowering of oxygen request. This is due to the frequency reduction and to the changes in cardiac metabolism from fatty acid utilization towards aerobic glycolysis. Down regulation of beta-1 receptor is a typical phenomenon of heart failure due to exposition to elevated catecholamine levels. Carvedilol experimentally demonstrated to induce up-regulation of these beta-1 receptors. Other potential actions of Carvedilol are a recover in diastolic function, reduction in renin-angiotensin activity, increase in protein synthesis, antioxidant anti-proliferative and anti-inflammatory effects. All these actions contribute to ameliorate LV performance and cardiac work capacity.

Figure 2. Reduction of LV volumes and improvement of EF during Carvedilol treatment.
Although Carvedilol has multifaceted properties, its use is standardized in mild to moderate heart failure, but in advanced NY-HA classes and in elderly patients remains uncertain. The proportion of IV class is small and the benefit is not clear: the beta-blocker evaluation trial (BEST) failed to show a benefit in sicker patients. Recently two trials (Copernicus and Cibis II) showed an improvement in rate mortality and re-hospitalization also in more compromised patients. These studies answered to an important question about the tolerance, the beneficial and additional effect of beta-blocker. Even in these patients, Carvedilol demonstrated to reduce cardiac sudden death and adverse cardiac remodelling with good tolerance.

However some questions remain to be addressed: does this benefit extend to patients with ischemic and non-ischemic causes? Is the benefit for all races the same? What is the former mechanism that induces mortality reduction?

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 Cardiomyopathy) was the first 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, haemodynamic profile, EF, stress tolerance).

The most studied beta-blocker in heart failure is Carvedilol (Table II).

The ANZ trial (Australian New Zealand 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.

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 ethiology.

Table II. Major Carvedilol trials on heart failure.

<table>
<thead>
<tr>
<th>Trials</th>
<th>Cause of heart failure</th>
<th>Nyha class</th>
<th>Primary end point</th>
<th>Odds ratio</th>
<th>Risk reduction</th>
</tr>
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<tbody>
<tr>
<td>Metra</td>
<td>IDC</td>
<td>II-III</td>
<td>Hemodynamics</td>
<td>1.00</td>
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</tr>
<tr>
<td>Olsen</td>
<td>IDC/CAD</td>
<td>II-IV</td>
<td>Hemodynamics</td>
<td>1.34</td>
<td>–</td>
</tr>
<tr>
<td>US Carvedilol</td>
<td>IDC/CAD</td>
<td>II-IV</td>
<td>Hemodynamics</td>
<td>–</td>
<td>-65%</td>
</tr>
<tr>
<td>ANZ</td>
<td>CAD</td>
<td>I-III</td>
<td>Exercise tolerance, morbidity+mortality</td>
<td>0.75</td>
<td>-26%</td>
</tr>
<tr>
<td>E, Krum</td>
<td>IDC/CAD</td>
<td>II-IV</td>
<td>Hemodynamics</td>
<td>0.70</td>
<td>–</td>
</tr>
<tr>
<td>Bristow</td>
<td>IDC/CAD</td>
<td>II-IV</td>
<td>Exercise tolerance</td>
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<td>-73%</td>
</tr>
<tr>
<td>Packer</td>
<td>IDC/CAD</td>
<td>II-IV</td>
<td>Exercise tolerance</td>
<td>0.39</td>
<td>-65%</td>
</tr>
<tr>
<td>Colucci</td>
<td>IDC/CAD</td>
<td>II-III</td>
<td>Morbidity+mortality</td>
<td>0.22</td>
<td>–</td>
</tr>
<tr>
<td>Cohn</td>
<td>IDC/CAD</td>
<td>II-IV</td>
<td>Quality of life</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Copernicus</td>
<td>IDC/CAD</td>
<td>IV</td>
<td>Morbidity+mortality</td>
<td>–</td>
<td>-35%</td>
</tr>
<tr>
<td>Capricorn</td>
<td>CAD</td>
<td>I-II</td>
<td>Morbidity+mortality</td>
<td>–</td>
<td>-23%</td>
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IDC = idiopathic dilated cardiomyopathy; CAD = coronary artery disease.
gy (mostly dilatative cardiomyopathy) 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.

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 than the other major beta-blocker trials, so the results of risk reduction were too favourable (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

**Figure 3.** Difference in survival in non treated and treated patients.
favourable trend (total mortality, cardiovascular mortality, IMA, mortality due to heart failure or arrhythmias, hospitalizations).

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 cardiomyopathy 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 conditions47.

Carmen Trial (Carvedilol, ACE-inhibitor remodelling 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 remodelling in heart failure48.

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. Carvedilol has other synergetic effect:

- reduction of about 30% on global mortality
- reduction of sudden death
- improvement in EF (of about 30%), and in the NYHA class
- improvement in the exercise capacity

From all the examined data it is possible to say that the beta-blockers can improve haemodynamic parameters and these results are most pronounced for Carvedilol therapy, independently from the aetiology of heart failure and probably even in advanced NYHA class and in more compromised subjects3,50.

**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 β1-receptors.

Some favourable 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 metaanalysis in patients with mild to moderate peripheral vascular disease treated with β-blockers. The β-blockers did not worsen the peripheral disease31.

It is possible that compounds like Carvedilol, thanks to vasodilated activity a1-receptor-block related, could reduce this kind of side effect.

**Diabetes Mellitus**

β-blockers can reduce the peripheral sensitivity to insulin and modificate in unfavourable way the LDL-HDL equilibrium
in plasma\textsuperscript{52-56}. However, clinical trials showed that \(\beta\)-blocker therapy improvement in mortality and morbidity exceeded the negative influences on the glycemic and lipid risk profile\textsuperscript{57}.

In patients with heart failure, \(\beta\)-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 the muscles.

Another problem is that \(\beta\)-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 (sweatiness) seems to depend on the parasympathetic stimulation. Therefore, \(\beta\)-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**

\(\beta\)-blockers in patients with COPD and asthma must be used carefully. In asthmatic patients \(\beta\)-blockers-induced bronchoconstriction is conditioned by many and often unpredictable variables\textsuperscript{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 \(\beta\)-blockers therapy. Particularly, non selective \(\beta\)-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. \(\beta\)-blockers can be used when FEV1 is > 50\% of the predicted value, controlling the stability of ventilatory conditions.

**Bradycardia**

The use of \(\beta\)-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 \(\beta\)-blockers (favouring Carvedilol) reducing or suspending other drugs determining heart rate reduction if they are not tolerated all together\textsuperscript{60}.

**Hypotension**

We must be careful when hypotension is symptomatic or when systolic pressure is < 80-90 mmHg. Before contraindicating the use of \(\beta\)-blockers it’s necessary to increase the pressure by modifying the associated therapy\textsuperscript{61}.

**Atrial Sinus Knot Diseases**

\(\beta\)-blockers are able to neutralise electrophysiological effects of \(\beta\)-adrenergic stimulation improving the slope of the 4\textsuperscript{th} phase of action potential and increasing junctional conduction\textsuperscript{62}. So \(\beta\)-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**

\(\beta\)-blockers have a remarkable effect on junction conduction in proportion to the power of the used \(\beta\)-blocker and to the single dose administered. In particular, \(\beta\)-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\textsuperscript{62,63}.

**Alteration of Liver Function**

Carvedilol is highly lipophilic and it is metabolised in the liver and several metabolites are pharmacologically active. Its use is contraindicated when liver alterations are clinically evident\textsuperscript{64}.

**Kidney Diseases**

\(\beta\)-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 haemodialysis62,63.

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 rivaluated because the introduction of the new generation of this drugs (like Carvedilol) and the new knowledges permit a larger use and and a better prevedibility of the side effects53. In fact, 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 impairment65. 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 antischismic and anti hypertrophic actions for all ancillary molecular properties 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.

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