THE ADVANTAGES OF CARVEDILOL IN CORONARY ARTERY DISEASE

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Summary. Dilatrend (carvedilol) is a nonselective beta and alpha blocker with antioxidation and antiproliferative effects. These effects prevent mechanical damage of the endothelium of coronary arteries and have no negative influence on metabolic risk factors: lipid prophyl and insulin resistance. With beta-blockade, dilatrend (carvedilol) reduces the heart rate and blood pressure, with alpha-blockade it reduces the peripheral vascular resistance and in that way decreases the myocardial oxygen consumption and myocardial wall stress. Dilatrend (carvedilol) prolonges exercise limits (duration of exercise). Applied in the acute phase of myocardial infarction, dilatrend (carvedilol) increases the patients' survival rate, reduces new coronary events, and with antioxidation action it prevents reperfusion arrhythmias. With positive hemodynamic effects it improves the left ventricle function in patients with ischemic cardiomyopathy, and gives a chance for survival to the coronary patients who run high surgery risk.

Key words: Carvedilol, coronary disease, myocardial infarction

The effect of carvedilol upon the coronary arteries endothelium

The central position in the onset and the determination of the course of the coronary disease is occupied by the atherosclerotic plaque of the coronary artery. The initial event in the appearance of the atherosclerotic plaque is a chronic and gradual mechanical damage of the endothelium (hypertension, oscillations of heart rate, turbulent blood flow at certain points of the blood vessel or intervention manipulations). Hypercholesterolemia, glucolized end products in diabetes (mostly insulin-dependent), chemical irritants (tobacco smoke), circulating catecholamines, inflammatory processes (immuno complexes, infectants, free oxygen radicals) emphasize the already present damage of the endothelium. The damage of the endothelium results in the increased vascular permeability for lipids and monocytes. The receptor control of the accumulation of cholesterol is lost (mostly of LDL-a) which passively goes through the endothelial barrier, gets oxygenated by the free oxygen radicals. The expression of glucoproteins at the surface of the endothelial cells starts the activation of the macrophages that phagocyte the oxygenated LDL, there appears a bubbling "foam cell" - part of the nucleus of the atherosclerotic plaque. After the saturation with the lipids the macrophages can release a large number of chemotactic factors that further activate the monocytes, enzymes and free oxygen radicals and thus emphasize the damage of the endothelium and the destabilization of the plaque. (1).

In the prevention of the onset of the coronary disease we strive to maintain the function and the integrity of the endothelium of coronary arteries, primarily by controlling the variable risk factors. Today, by using a particular drug it is possible to influence most of the mentioned processes that lead to the damage of the endothelium and the onset of the atherosclerotic plaque. Carvedilol is a non-selective β blocker and α blocker that by controlling the (size and oscillation) of the blood pressure, heart rate, prevents the mechanical damage of the endothelium.

Circulating catecholamines through numerous β receptors demonstrate a toxic effect on the endothelium of human coronary arteries which results in the apoptosis of the endothelial cells. (By the mechanisms of calcium overload of the endothelial cells, by releasing free oxygen radicals, by increasing the permeability of the sarcolemes and by the increased concentration of cAMP). Carvedilol and atenolol reduce the epinefrin-induced lipid peroxidation of the endothelial sarcolemes, where carvedilol is significantly more powerful in comparison with atenolol in the equimolar concentration of the medicament (p<0.05). The powerful antioxidation effect of carvedilol is considered responsible for this superior antiapoptotic effect compared to other selective β1-blockers (2). Compared to propranolol, carvedilol is a ten times more powerful antioxidant (3).

Oxygenated LDL damages the endothelium by cytotoxic products of lipid peroxidation, emphasizes the release of vasoconstrictor substances from the endothelial cells and at the same time it activates the macrophages. With its antioxidation characteristics carvedilol prevents the harmful influence of free oxygen radicals on the endothelium itself and also prevents the oxidation...
of LDL cholesterol particles. Yue and Feuerstein experimentally demonstrated the protective effect of carvedilol on the cultivated endothelial cells of the umbilical vein exposed to the effect of free oxygen radicals. Carvedilol inhibits the activation and adhesion of neutrophils at the damaged endothelium of coronary arteries (3).

At the place where the endothelium is damaged the production of the endothelial factors of relaxation is reduced, while the synthesis of factors of vasoconstriction is increased. Apart from the protective effect in relation to the function and morphology of the endothelium by blocking the α receptors carvedilol prevents the repetition of the vasospastic reaction of coronary arteries which would contribute to the damage of the endothelium. The liposolubility of carvedilol correlates with its antioxidation potential as well as with its antiatherogenic effect (4).

Vascular smooth muscle cells, which migrate into intima during the atherosclerotic processes can produce endothelial factors of vasoconstriction (ET-1, ET-2, ET-3), which synergistically with angiotensin II increase the vascular tonus, proliferation and the growth of the cell (5). At the same time proliferation and migration of smooth muscle cells of intima contribute to the increase of the plaque and to remodelling of the blood vessel, so the significance of the antiproliferation effect of carvedilol in preventing the onset and progress of coronary disease comes to the foreground. Experimentally proved, the antiproliferative effect of carvedilol is manifested via its metabolitethes M14 and M21. Carvedilol inhibits the proliferation of the cells of the vascular smooth muscle of the rat stimulated in vitro by various mitogenes, unlike celiprolol, sotalol and labetalol.

**Carvedilol in the stable angina pectoris**

When the atherosclerotic plaque of the coronary artery appears, the aim of the therapy is to prevent the growth and maintain the stability of the plaque.

Carvedilol prevents oscillations of heart frequency and blood pressure and thus prevents the mechanical destabilization of the plaque.

With its antioxidation effects it inhibits the gathering of macrophages and the effect of their proteolitic enzymes, which decompose the fibrous cap of the plaque. By inhibiting the oxidation of LDL cholesterol particles it prevents the growth of the lipid nucleus of the plaque and of its destabilization as well (6). By beta and alpha blockade, carvedilol reduced the myocardial oxygen consumption, thereby reducing the ischemia risk. Non-selective beta-blockers can increase the peripheral vascular resistance by inhibiting vasodilatation through blocking beta-2 receptors. With the additional alpha blockade carvedilol contributes to the peripheral vasodilatation, with which its reduces the myocardial wall stress and the energy demand. It doesn't have the intrinsic sympathetic activity (ISA) nor does it increase the oxygen demand during the night (7).

With its chemoreologic effect it improves the myocardial perfusion and prevents the appearance of the thrombus. Applied at the dose of 10-20 mg per day, carvedilol reduced in vitro blood viscosity, aggregation of thrombocytes (8). The decrease of blood viscosity improves the flow degree, reduces the risk of the destabilization of the plaque by blood currents.

Carvedilol doesn't show a significant influence on the metabolism of carbo-hydrates, and is a suitable medicament for treating the coronary disease in diabetic patients. (9).

Unlike other beta-blockers carvedilol doesn't show undesirable effects on the lipid profile and thus doesn't have a negative influence on the progression of the atherosclerotic process.

In the group of 15 patients with the chronic, stable angina pectoris it was shown that, compared to placebo, a 25 mg dose of carvedilol od 25 mg significantly prolongs the total duration of exercise as well as the time until the appearance of the ST segment depression of 1 mm (10).

Further placebo-controlled studies have shown that carvedilol reduced the incidence of symptomatic and asymptomatic myocardial ischemia (11,12). The studies by Das Gupt (12), Jamal (13), show that carvedilol shows the antiischemic effect and considerably increases the threshold for the onset of the effort-induced ischemia.

All the three doses of carvedilol (12.5; 25; 50 mg twice per day) prolong the time until the appearance of the depression of the ST segment of 1 mm at the ECG, but the significance of the difference, compared to placebo, increases with the dosage (14).

Apart from the antiischemic effect, carvedilol has been shown to affect the parameters of the function of the left ventricle in patients with stable angina pectoris. Carvedilol in the dose of 25 mg ×2 and 50 mg ×2, during the two-week treatment significantly reduces the end-systolic and end-diastolic volume of the left ventricle compared to placebo (p<0.001 and p<0.0001), where the significance increases with the increased dose of the medicament. Carvedilol significantly increases the peak of the degree of the left ventricle filling (EDV/sec) and the first third of the filling fraction, by which it improves the diastolic performances of the left ventricle (15). Lahiri was among the first to show, in a group of patients with the stable angina pectoris and the damaged function of the left ventricle at the rest, that carvedilol (25 mg once per day, and then 50 mg twice per day during two weeks) improves the ejection fraction (EF) from 40±4% to 48±8% (p<0.05) (15).

It was shown that the combination of propranolol + isosorbid-dinitrata (ISDN + P) had a greater acute antiischemic effect at exercise, compared to carvedilol. Afer 6 months of therapy, the time until the appearance of the ST segment depression of 1 mm and the total duration of exercise, did not considerably differ in the group treated with the placebo and the ISDN + P combination, while the antiischemic effect
of carvedilol has been retained during the study period. It is considered that the development of tolerance to ISDN is responsible for the decrease of the efficiency of the mentioned combination of medicaments (16). The studies by Watanaba show that antioxidant characteristics of carvedilol prevent the onset of nitrate tolerance during a continuous nitroglycerine therapy unlike arotinolol that doesn't have antioxidant characteristics (17). The metabolite of carvedilol BM920228, inhibits the development of nitrate tolerance, contributes to the nitrate-induced vasodilatation and by reducing the oxidation stress it reduces the activity of thrombocytes (18).

Comparing the effect of metoprolol and carvedilol it was shown that both medicaments considerably prolong the time until the appearance of the symptoms or of the depression of the ST segment of 1 mm in the test using the physical exercise of the patients with stable angina pectoris, where the effect of carvedilol was greater (19). This advantage of carvedilol sombody explained by its antioxidant effect on the improvement of the function of the coronary endothelium artery an a more adequate response during effort (20).

Carvedilol is a more efficient antiischemic medicament compared to verapamil (21) and the slow-releasing nifedipin (22). The total number of undesired effects was greater in the group of patients treated by verapamil (58.2%) compared to carvedilol (48%).

Carvedilol in unstable angina pectoris

Destabilization of the coronary plaque creates conditions for thrombus forming and a considerable reduction of the coronary flow. The aim of the therapy in the acute coronary syndrome, of the unstable angina pectoris type is to prevent the growth of the thrombus and to stabilize the plaque. Carvedilol normalizes the concentration of beta-thromboglobulin, thrombocytes factor-4, thromboxan B2, inhibits the aggregation of thrombocytes, thus reducing the possibility of forming of the thrombus at the dynamic destabilized plaque (23). Carvedilol improves the fibrinolitic response of the endothelium to anoxia, reduces the blood viscosity and reduces the possibility of the aggregation of thrombocytes (24).

Carvedilol in the dose of 50 mg per day, added to aspirin, intravenously applied nitrates and heparin, considerably reduce the frequency and the seriousness of ischemic events compared to placebo in the double blind study in the group of 116 patients with unstable angina pectoris. The frequency of repeated ischemia was 15% in the carvedilol group compared to 25% in the placebo group (p<0.05) (25).

The efficiency of carvedilol in the prevention of restenosis after the coronary angioplastics was shown in the study that included 276 patients subjected to PTCA, where the restenosis appeared in 4.2% if the patients received carvedilol (25 mg 2 × per day) 6 months after the intervention, i.e. in 18.5% patients receiving the placebo (26). The EUROCARE (European Carvedilol atherectomy restenosis) study aims at showing the effect of the carvedilol therapy (25 mg twice per day) during 6 months compared to the placebo in the prevention of restenosis, after a successful directional coronary atherectomy, with or without complementary angioplastics (serruys PW. Personal communication in Maqueda). The results of the study have not been published.

The advantages of carvedilol in the acute phase of the myocardial infarction

With the occlusion of the coronary artery, which lasts long enough, there appears the acute myocardial infarction (AIM). The aim of the therapy in AIM is to achieve, as early as possible, the reperfusion of infarct-related artery (by thrombolysis), retain its passability (by anticoagulant and antiaggregation therapy) as well as to maximally limit the size of the infarction.

Beta blockers applied in early hours of AIM aim at reducing the size of the myocardial infarction and the frequency of the disturbance of the heart rhythm (27). This effect of β blockers is achieved by reducing the myocardial oxygen consumption (through the reduction of heart rate and blood pressure) and reducing the ischemia, that is, by the rapid alleviation of pain.

The effect of β blockers in AIM can be divided into the acute ones (when the medicament is given early in the development of the infarction) and long-term ones (the secondary prevention), when the medicament is applied after the acute phase of the infarction.

During the first 24 hours from the appearance of the chest pain in AIM there is a considerably increased secretion of catecholamines. The intravenous application of β blockers reduces the effect of catecholamines (CTH) on heart rate and blood pressure (which thus reduces the myocardial oxygen consumption), reduces the circulating level of free fatty acids by antagonizing the lyposoluble effect of catecholamines and at the same time reduces the incidence of arrhytmias. Comparing the effects of beta-blockers, it has been experimentally shown that carvedilol is significantly more efficient in reducing the size of the infarction compared to propranolol, celiprolol and diltiazem (28).

The advantage of carvedilol over other beta blockers can also be found in the fact that the acute beta blockade in AIM can cause a deeper ischemia caused by neurohormonal activation and vascular constriction through the non-blocked alpha-receptors (29). With the simultaneous beta and alpha blockade carvedilol improves the subendocardial flow and reduces the myocardial ischemia.

In AIM the density of beta receptors increases for about 25-30%. Unlike metoprolol, carvedilol due to its characteristic of specific binding to beta receptors (guanine nucleotide modulatable binding) does not lead to the increase of the density of beta receptors in the myocardium and enables the complete sympathetic antagonism without the unfavourable effect of the CTH on the CNS (30). Circulating catecholamines increase the
aggregation of thrombocytes, the release of the powerful vasoconstrictor thromboxan A2 that increases the resistance in the coronary microcirculation. The increased tonus of SNS and the concentration of CTH lead to the increase of the coronary tonus, the inability of vasodilatation of microcirculation and the deterioration of myocardial perfusion. With the blockade of \( \alpha \) receptors, carvedilol achieves the prevention of the appearance of vasoconstricting of microcirculation and enables the adequate perfusion of the myocardium after the recanalization of the infarct-related artery, it also achieves the reduction of the peripheral vascular resistance and reduces the afterload of the left ventricle, which reduces the myocardium wall stress and the expansion of the infarction.

With its strong antioxidant effect carvedilol neutralizes the activity of free oxygen radicals and prevents reperfusion damages of the myocardium, limits the size of the infarction by inhibiting the migration of polymorphonuclear leucocytes towards the necrosis area.

Until now in the thrombolytic era, there have been a few large studies of the application of beta-blockers in AIM. ISIS- I and GUSTO studies show that atenolol applied in the acute phase of myocardial infarction reduces mortality, but also increases the frequency of shocks, congestive heart failure and the need for pacing as the result of the antagonism of sympathomimetic stimulation (31). TIMI II study has shown that metoprolol applied in the acute phase of the myocardial infarction together with the thrombolytic therapy reduced the frequency of new coronary events and reinfarction but without affecting the improvement of the patients' survival (32).

The negative inotropic effect limits a wide use of beta-blockers in AIM, especially in the group of risky patients, with the damaged function of the left ventricle. The favourable effect of metoprolol (33) and bisoprolol (34) has been manifested mostly in the dilatation cardiomyopathies. Therefore Basu supposed that carvedilol with its characteristics would be a safe medicament to apply intravenously in most AIM patients, including the group of patients with a mildly serious heart insufficiency (35). The primary aim of CHAPS (Carvedilol Heart Attack Pilot Study) study (36) was to compare a group of AIM patients treated with carvedilol to a group of patients treated with placebo until the moment of the appearance of one of the serious cardiovascular events. The other aim was to show the safety of the medicament in comparison to the undesirable effects, as well as its influence on the functional capacity, hemodynamics, systolic and diastolic function of the left ventricle in the group of patients admitted at the coronary ward with typical signs and symptoms for AIM. The patients with NYHA class IV or the cardiogenic shock, heart rate <45/min., hypotension, AV block II-III, creatinine >159 µmol/L were excluded.

All the patients received Aspirin and SC heparin for threedays. It was up to the admittance doctor to decide on the thrombolysis. Within 24 hours from the start of the pain, the patients were IV treated with 2.5 mg of carvedilol or the placebo during 15 minutes. It was followed by the oral dose of 6.25 mg of carvedilol or placebo 4 hours after the injection, and then 6.25 mg 2× per day during 2 days. The dose was increased to 12.5 mg 2× per day on the third day of the therapy and was retained at 12.5 mg - 25 mg 2× per day during the whole study (6 months) or the onset of a CVS event that marked the end of the study when the medicament was terminated. The adjustment of the dose was done on the 14th day, when carvedilol was increased from 25 mg 2× per day if TA was >120/95 mm Hg and HR at least 55 beats in a minute. The end of the study was defined by: heart death, reinfarction, USAP, heart insufficiency, urgent revascularization, ventricular arrhythmia, CVI, or the need for the additional CVS therapy (ACE inhibitors have not been routinely applied for the asymptomatic dysfunction of the left ventricle.)

In the group of AIM patients, treated with carvedilol the frequency of serious cardiac events (reinfarctions, unstable angina, urgent revascularization) was reduced for 42%, which was a significantly larger percentage compared to the placebo-treated group (p<0.03). Despite a large number of patients with heart failure the applied carvedilol was well-tolerated. The patients treated with carvedilol showed a significant improvement of EF compared to the placebo group (p<0.05), the lowering of the systolic volume of the left ventricle (p<0.03), the increase of the stroke volume (p<0.01), a considerable improvement of the E/A ratio as the parameter of the diastolic function (p<0.001) and of the improvement of the left ventricle filling, which proved a favourable effect of carvedilol on the improvement of the function of the left ventricle in AIM patients. The group treated with carvedilol showed the improvement of the regional wall motion abnormalities (p<0.001), both in and outside the infarction zone. This difference turned out to be significant already on the seventh day of the carvedilol therapy and in the following 6 months of treatment. With the break of the carvedilol therapy, despite the application of other antiischemic medicaments (atenolol, diltiazem or nicardipine) there appear new cardiovascular events, so the survival curves start to converge and the significant difference between the carvedilol-treated group and the placebo-treated group of patients is lost. This showed that the antiscemic effect is important in the acute phase of the infarction but also in the retaining and improving of the function of the saved myocardium (by thrombolysis) which is viable but still at high risk from new coronary events.

In the subgroup of patients with EF <45% that experienced AIM, after 3 months of carvedilol therapy there appears a significant reduction of end-systolic (p<0.01) and end-diastolic volume (p<0.01) of the left ventricle compared to the placebo group. The sum of the segmental motions and the ejection fraction have been
significantly improved in the group of patients with AIM and the dysfunction of the left ventricle after three months of carvedilol therapy. The results of this study pointed at the favourable effect of carvedilol on the process of remodelling of the left ventricle after AIM in the group of patients with the left ventricle dysfunction and gave the guidelines for further research.

The importance of carvedilol in the remodelling prevention in patients with the left ventricle dysfunction after the acute myocardial infarction

The chief determinant of the prognosis for patients after AIM is the function of the left ventricle (37), which is determined by the loss of functional myocardium (affected by necrosis), residual ischemia, the worsening effect of the pathological remodelling.

Remodelling after AIM is a progression of the changes in the size of the left ventricle, the shape, thickness of the myocardium, including the infarction and non-infarction segments. The process of ventricular remodelling is influenced by the size of the infarction, the healing of the infarction area, residual ischemia, the overload of the left ventricle (the pressure of expanding of the left ventricle, the inotropic condition of the left ventricle, the heart rate and the neuroendochrine activity,) the increase of the total ventricular mass and the change of the geometry of the left ventricle. The prevention or the slowing down of the remodelling of the LV after AIM, are an important therapeutic goal.

The result of the acute reperfusion (thrombolysis) is saving of the myocardium and the limitation of the infarction size, which at the same time means the prevention or slowing down of the remodelling process. It is known that ACE inhibitors improve the prognosis after AIM mostly because of their favourable effect on the process of remodelling of the left ventricle.

Favourable results of carvedilol application in AIM patients with the damaged left ventricle function pointed at the possible role of carvedilol on the remodelling index. The goal of Senior et al. (38) was to show a favourable effect of carvedilol on some additional markers that are at the basis of the changes of the left ventricle volume – the reduction of the area of abnormality of the wall thickening at the infarction point, the reduction of the wall thickness of the left ventricle in non-infarction segments and the total mass of the left ventricle and the favourable change of the geometry of the left ventricle. The patients selected for this study are part of the mentioned CHAP study, with the same protocol of patients' treatment. Two-dimensional echocardiography was performed before the patient was released and three months after AIM.

The results of the study showed that in the group of patients who were treated with carvedilol for three months there was a significant reduction of the thickness of the myocardium in non-infarction areas, the reduction of the total mass of left ventricle, the decrease of abnormality of regional kynethics in the infarction area, and the improvement of the sphericity index, which differed from the placebo-treated group. In this way it was shown that carvedilol has an essential, protective effect on the progressive remodelling of the left ventricle after the acute myocardial infarction, which is related to the significant reduction of the frequency of new coronary events in the group of carvedilol-treated patients. The mechanism at the basis of the slowing down/prevention of remodelling by carvedilol is multifactorial. Unlike the conventional β blockers, carvedilol by alpha blockade causes the reduction of the left ventricle filling pressure, reduces the myocardial wall stress, oxygen consumption. Apart from the hemodynamic effects, with the neurohumoral effects it reduces the myocardium mass, the volumes of the left ventricle, and improves the left ventricle function.

It is considered that the effect of carvedilol is even underestimated, because it is applied on the first day of AIM, and the echocardiogram was not performed earlier than 5-7 days. Dought et al. (39) in the independent study showed that carvedilol reduces the size of the left ventricle after 6 months of treatment in patients with congestive heart failure caused by the myocardium disease and thus improves the prognosis of such patients.

It is the safety of its application even in patients with Killip class II and III, with the evident heart failure after AIM that accounts for the advantages of carvedilol. Carvedilol has been shown to be uniquely suitable for the therapy of high-risk patients after AIM.

This resulted in the first, prospective, randomized, double-blind placebo controlled CAPRICORN study (with 1900 patients) whose aim was to examine the influence of beta-blockers (carvedilol) on the morbidity and mortality in the high-risk group of patients, with the left ventricle dysfunction after AIM (40). The criteria for the including into the study are the AIM diagnosis within the last 21 days, ejection fraction (EF) of the left ventricle ≤40% measured by 2D echocardiography, radionuclide or contrast ventriculography, the score of segment motility (WMSI) < 1.3. All the patients are also treated with the ACE inhibitors. The results of the study have not been published yet.

The effect of carvedilol on the improvement of the hybernated myocardium function in patients with the left ventricle dysfunction of ischemic origin

In the group of coronary patients with heart failure the improvement of the ejection fraction under the influence of beta-blockers and ACE inhibitors is of heterogenous origin unlike the response obtained in patients with dilatation cardiomyopathy. The ratio between the dose of the medicament and the EF increase is less prominent in coronary patients.

One of the mechanisms with which beta-blockers improve the left ventricle function are the prevention of myocardium ischemia, that is the postischemic myocardial dizziness. Hibernation means a functional and metabolic 'down', a regulated protective mechanism in order to retain the myocyte viability. It is thought that in the appearance of the myocardium hibernation the repeated dizziness are important in the circumstances of
the reduction of blood flow below the threshold necessary for retaining the normal myocyte function.

By reducing the coronary style in the zones surrounding the ischemia or the subendocardium, by prolonging the diastolic coronary flow and reducing the metabolic demand of the surrounding myocardium, β blockers increase the flow into the zones of the hibernated myocardium. The blockade of α₁ and β₁ and 2 receptors with carvedilol has its advantages because it protects a wider area of adrenoreceptors from the catecholamine excess. The blocking of α receptors achieves the coronary vasodilation that can further improve the myocardial blood flow, the peripheral venous and arterial dilatation reduce the pre- and after-load. The protection of the ischemic myocardium from free oxygen radicals provides additional mechanisms, with which carvedilol can regain the function of the dizzy and hibernated myocardium and prevent heart failure.

After successful thrombolysis, the patients run the further risk of possible new cardiac events and heart failure. The residual ischemia is the risk for repeated acute coronary syndromes, but also the area of the still vital myocardium. Basu et al. in 1996 showed that the carvedilol treatment significantly reduced the onset of new coronary events (compared to the placebo p<0.04), in the group of patients with TI-201 proved reversible ischemia, 6 weeks after the application of thrombolysis in AIM (41). This study clearly demonstrated the antiischemic and protective effect of carvedilol in the group of patients treated by thrombolysis in AIM. Experimental studies showed that carvedilol in the instances of ischemia and reperfusion reduces the number of apoptotic myocytes in the ischemic area for 77%, with the effect independent of beta-blockade (42).

The patients with a large area of the ischemic or hibernated myocardium can respond to the β blockers therapy in a similar way as the patients with dilatation cardiomyopathy, unlike the left ventricle function that is mostly determined by the postinfarction scar.

Having in mind the importance of the retention of the vital myocardium after the acute infarction, CHRISTMAS-(43) study was started with the aim of determining whether the presence of hibernation of the myocardium in coronary patients with the left ventricle dysfunction (EF<40%), predicts the degree of improvement of the left ventricle, by application of carvedilol compared to placebo.

The patients were divided into groups with or without hibernated myocardium. The diagnosis of hibernation was based on the mismatch between the echocardiographically detected abnormality of wall motility and the radioisotopic myocardial perfusion scan, at rest by using Tc 99m sestamibi.

Orally applied carvedilol was adjusted until the goal dose of 25 mg., twice per day for the patients weighing up to 85 kg, or 50 mg 2x per day if the patient weighed more than 85 kg.

It is believed that this study will help the identification of the hibernated myocardium as the specific goal for the medicament treatment among the patients with heart failure. Also, it will provide the answer as to whether revascularization is really necessary for the patients with the hibernated myocardium.

The detection of ischemia, hibernation, dizziness among the patients with heart failure can identify the group of patients that benefit from the beta blockers treatment. The patients in whom the left ventricle function was not improved by the carvedilol therapy can be protected from lethal arrhythmias and recurrent infarctions by their β blocking effects and this still achieve clinical benefits.

The seriousness of the left ventricle dysfunction is the determinant of the operational mortality, and improved by beta-blockers before the cardiosurgical intervention it can reduce the surgical risk.

The results of CHRISTMAS study should suggest whether the medicament treatment for the dizzy and/or hibernated myocardium (potentially reversible contractile dysfunction) is the addition or the alternative to revascularization, especially in cases when revascularization is not the acceptable solution.

**Carvedilol and the quality of life of coronary patients**

Health-Related Quality of Life means the physical felling of well-being that affects psychological and economic aspects of life, social and family interaction (44). With its antiischemic effect carvedilol reduces the seriousness and the number of anginal attacks, increases the threshold for the effort-induced ischemia and improves the functional capacity of the coronary patient, thereby providing the active professional life, realistic insight into the restrictions caused by the disease (with the termination of the medicament the symptoms and the signs of the disease get worse). Carvedilol therapy improves the ejection fraction of the left ventricle, the symptoms and signs of heart failure, which affects the adequate psychosocial adaptation and the quality of life in restriction circumstances caused by the coronary disease (45).

**Conclusion**

Dilatrend (carvedilol) is an efficient antiischemic medicament that increases the threshold for the effort-induced ischemia, and reduces the number of asymptomatic ischemic episodes. Dilatrend (carvedilol), applied in the early stage of the myocardial infarction reduces new coronary events and the patients' mortality, prevents the left ventricle remodelling. It improves the left ventricle function in patients with ischemic cardiomyopathy and the quality of life of such patients. The results of new studies will show whether by improving the function of the hibernated myocardium, dilatrend (carvedilol) can bridge the period until revascularization or it can be the alternative in patients with high surgery risks.
References


40. CAPRICORN-Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction-Original trial design

PREDNOSTI KARVEDILOLA U KORONARNOJ BOLESTI

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