

AN ACCOUNT OF A SEVEN YEAR EXPERIENCE WITH CARVEDILOL AND AMIODARONE IN SEVERE CONGESTIVE HEART FAILURE PATIENTS WITH SINUS TACHYCARDIA

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Summary. *The aim is to report on a rationale for amiodarone and carvedilol combination in severe congestive heart failure with sinus tachycardia, because there are very few reports on this topic in available medical literature. We analyzed 112 patients with NYHA III/IV congestive heart failure, with coronary artery disease in two thirds. There were 59 males and 53 females, aged 64 ± 9 years, from March 1996. The average initial dose of Amiodarone was 860 ± 95 mg, and maintenance dose was 285 ± 140 mg. Carvedilol was introduced in dosage of 6.25 mg, and kept at 28 ± 13 mg. Patients were followed from 2 months to 6.5 years (average 1.7 years).*

Results: *The heart rate was reduced with amiodarone either intravenously or sublingually from 130.2 ± 4.9 to 94.0 ± 7.4 /min. ($P < 0.0001$) in 2 days. Following recompensation in 5-10 days carvedilol was added and the heart rate diminished further, from 94.0 ± 7.4 /min. to 81.0 ± 3.6 /min. ($P < 0.0001$). The decrease in the rehospitalization rate was obvious. In our 1st patient (and among the first ones in the country), the left ventricle end-diastolic diameter = 80 mm and ejection fraction = 30% remained unchanged for 5 years. Side effects attributed to amiodarone and carvedilol combination: mild hypothyroidism (9 patients), AV block I^o (16 patients), QTc prolongation without torsade (34 patients) and INR control problems (32 patients).*

Conclusions: *1) There is a rationale for combining amiodarone and carvedilol in severe congestive heart failure and sinus tachycardia: to diminish oxygen consumption by decreasing the heart rate and afterload, to prolong diastole (and thus both left ventricle filling and coronary artery filling), with consequent ischemia suppression and reverse remodeling; to prevent both atrial fibrillation and ventricular tachycardia / fibrillation. 2) Amiodarone can be applied immediately and carvedilol following recompensation. 3) The risk / benefit ratio of amiodarone and carvedilol combination is quite acceptable.*

Key words: *Amiodarone, carvedilol, congestive heart failure, sinus tachycardia*

Introduction

Amiodarone is a unique antiarrhythmic. It has activities typical of each Vaughan - Williams class (dominantly third class). Thirty years ago, it used to be applied as antianginal agent. Amiodarone is the only "pure" antiarrhythmic (other than beta - blockers), that may improve survival after acute myocardial infarction and/or in congestive heart failure (1-6).

Amiodarone has been believed to have antifibrillatory effect (7), which is very desirable in congestive heart failure and/or acute myocardial infarction patients, who are prone to ventricular tachycardia / fibrillation. Amiodarone is more effective than lidocaine in the treatment of shock - resistant ventricular tachycardia (8). According to Brembilla-Perrot et al. (9), amiodarone is the main drug used in the treatment of ventricular arrhythmias: contrary to past guidelines, amiodarone is included in "The 2000 advanced cardiovascular life support guidelines" as a possible agent for hemodynamically stable monomorphic ventricular tachycardia,

non-QT prolonged polymorphic ventricular tachycardia, and ventricular fibrillation / pulseless ventricular tachycardia (10).

The results of the ARREST (Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias) trial prove amiodarone to be the antiarrhythmic of choice for ventricular fibrillation / pulseless ventricular tachycardia (10). Data on amiodarone support the use of these drugs in out-of-hospital resuscitation efforts (11).

Its efficacy is excellent in supraventricular arrhythmias, including atrial fibrillation, the most common chronic arrhythmia (12-17). Amiodarone prevents recurrences of atrial fibrillation even better than class I antiarrhythmics, which produced higher mortality than placebo in CAST trial. Other antiarrhythmics have a worse short term safety profile (1, 18-20). For example, propafenone has a more pronounced negative and proarrhythmic effect (especially in congestive heart failure, as well as in coronary artery disease, which is the most frequent cause of congestive heart failure). Quinidine is less safe (21, 22) and can increase mortality after longer application, etc.

Recently, we introduced a new indication for amiodarone: reducing the heart rate in sinus tachycardia in patients with severe heart failure (23). The lowering of the heart rate often can not be done using digitalis alone, and other antiarrhythmics are contraindicated in severe congestive heart failure because of negative inotropic action.

Carvedilol is also unique in having beta and alfa adrenergic receptor blocking capabilities together with pronounced antioxidative effect. It decreases peripheral vascular resistance, due to alfa receptor blockade. Carvedilol has been shown to have beneficial effects in most important diseases in cardiology: arterial hypertension, coronary artery disease, congestive heart failure and dysrhythmias. Carvedilol is indicated in stable angina pectoris patients, in whom carvedilol (25 to 50 mg twice daily) improves exercise capacity better than metoprolol (50 to 100 mg twice daily) (24).

In addition, carvedilol may prevent remodeling after an acute myocardial infarction. In The US Carvedilol Program, in 1094 congestive heart failure patients, carvedilol reduced total mortality by 65%, including patients in NYHA IV class (25). Carvedilol has one of the most important places in the congestive heart failure treatment (26, 27). It prolongs life and it seems to be the dose-dependent action, because being on a higher dose of carvedilol conveyed a survival advantage compared with being on a minimal dose, as shown in MOCHA trial (28). No other drug with beta blocking action has such result, including metoprolol. For example, in patients with dilated cardiomyopathy, who were poor responders to chronic metoprolol, the carvedilol treatment was associated with favorable effects on left ventricle systolic function and remodeling as well as on ventricular arrhythmias, whereas it had a negative effect on peak oxygen consumption (29).

Carvedilol was the first (dominantly) beta-adrenergic receptor blocker approved by the US Food and Drug Administration for the treatment of congestive heart failure, because it has been shown to reduce morbidity and mortality in patients with NYHA Class II or III (30). The COPERNICUS (Carvedilol Prospective Randomized CUMulative Survival) trial was halted because its Data and Safety Monitoring Board unanimously agreed that survival in the active treatment arm with carvedilol (even in NYHA IV congestive heart failure class) was significantly superior to the treatment with placebo (31). Most authors suggest carvedilol after resolution of the decompensated phase of congestive heart failure, but there have been evidences for beneficial effects of carvedilol even in NYHA class IV congestive heart failure patients (32). Besides, the cost effectiveness of carvedilol for congestive heart failure compares favorably to that of other generally accepted medical interventions (33).

The aim of the study is to report on safety of combined application of carvedilol and amiodarone in congestive heart failure patients in sinus rhythm, without ventricular tachycardia on routine ECG.

Patients and methods

There were 112 consecutive congestive heart failure patients analyzed, the majority of whom were hospitalized in the Cardiovascular Department for last 7 years. There were 59 males and 53 females, aged 64 ± 9 years. The etiologic factors were: ischemic and / or hypertensive cardiomyopathy, idiopathic cardiomyopathy and aortic valve disease. NYHA class was III or IV in all patients. The left ventricular ejection fraction $\leq 30\%$ was the selection criterion. All patients had sinus tachycardia. Amiodarone was applied irrespective of "ambient" ventricular tachycardia on the ECG. The therapy was: loop diuretic with spironolactone / K^+ supplement, ACE inhibitor in maximal dose which was tolerated, nitrate and/or molsidomine, magnesium, digitalis, aminophylline, often tranquilizer, rarely dopamine/ dobutamine and exceptionally amlodipine. Not a single patient used first-generation calcium antagonists (verapamil, nifedipine, diltiazem), because of the negative inotropic action and chances to enhance the mortality (28). The patients were anticoagulated with the low – molecular – weight heparin (LMWH) overlapped with warfarin (34). All coronary artery disease patients had also aspirin 75-150 mg daily all the time. Ranitidine was applied for the prevention of gastrointestinal bleedings.

Carvedilol and amiodarone (Zdravlje) were used. Amiodarone was usually given in loading doses, sublingually in the majority of patients (23). This is the faster way to obtain the effective amiodarone concentrations than per os application. To our experience, the sublingual route of amiodarone administration permits the lower total dose and the shorter hospitalisation. In some patients with arterial hypertension i.v. route of application was chosen, when there was a pronounced need for rapid onset of action.

Amiodarone has been known for the large - scale of the unwanted effects (28). Thus, our practice has been to ensure the absence of hypokalemia, the prolonged QTc, the hepatic, thyroid and pulmonary lesions (except the chronic obstructive lung disease in 2 patients).

Amiodarone was given 400 - 600 mg s.l., followed usually with 200 - 400 mg per os. The dosage was individualized, according to the heart rate. We attempted the faster rate reduction in the patients with the coronary artery disease, aiming to reduce the chances for ischemia. On the other hand, we tried to avoid the excessive heart rate reduction, in order to allow the heart rate to compensate for the diminished stroke volume.

To provide the maximal safety, carvedilol was given after the resolution of decompensation. Introduction of carvedilol without previous amiodarone was felt unlikely - due to the potential worsening - in all our patients. The suggested doses are 3.125 b.i.d., but we have practiced to apply only 3.125 once daily and to control blood pressure and ECG daily (in hospitalized patients) or every 2nd-3rd day (in ambulant patients). The lower limit for systolic BP was 110 mmHg in the absence of signs of the hypoperfusion. This limit was higher (and

safer) than 85 mmHg as Kasper reported (28).

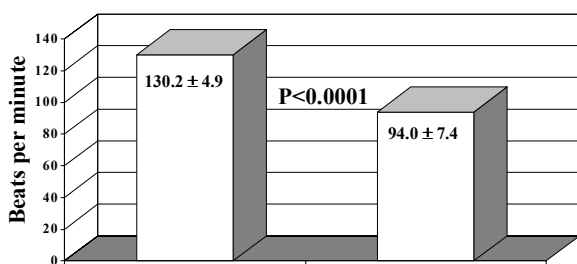
The increase in carvedilol dose was individualized, but usually the doses were enhanced weekly.

Results

Amiodarone was given in the decompensated phase, to achieve the faster stabilization.

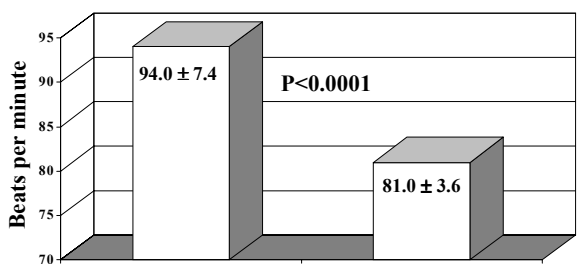
There was an impressive heart rate decrease with amiodarone in all our patients. In first days we diminished the heart rate to app. 100 beats per minute (bpm), allowing the heart rate to compensate for decreased stroke volume. The heart rate lowering had to be more rapid in the patients with ECG ischaemia and/or chest pain.

The heart rate was reduced from 130.2 ± 4.9 to 94.0 ± 7.4 bpm ($P < 0.0001$), in 2 days), as a result of the heart unloading and amiodarone (Graph 1).



Graph. 1. Heart rate 48 hours from the beginning of the therapy for the congestive heart failure

In 2 weeks the heart rate decreased from 94.0 ± 7.4 bpm to 81.0 ± 3.6 bpm ($P < 0.0001$) (Graph 2).



Graph. 2. Heart rate two months from the beginning of the therapy for the congestive heart failure

No influence on the blood pressure was observed. The decrease in the number of hospitalizations was easily recognized, and the majority of our patients stayed out of hospital for the whole follow-up.

Following the resolution of the decompensation carvedilol was added. The average time to carvedilol introduction was 8.5 ± 2.7 days.

Amiodarone dose was tapered slowly and carefully.

Amiodarone was stopped in the stable patients without the atrial fibrillation and the ventricular tachycardia, with heart rate < 80 bpm. There were 69 such patients.

At this time the dose of carvedilol was increased for 20-30%. Not a single unwanted effect was found then. Thus, in stabilized congestive heart failure patients withdrawal of amiodarone was safe in the presence of carvedilol. This is in part due to long elimination time of amiodarone.

Individual rehospitalization rate decrease was obvious. Among 48 patients with previous hospitalizations, individual time to the next hospitalization was prolonged from 40.6 ± 13.8 to 88.2 ± 32.3 days ($t = 9.38$, $P < 0.0001$). Free from rehospitalization were 13 patients (up to 5 years of follow up).

We titrated carvedilol dose up, according to the suggestions of dose - dependent benefit.

The low blood pressure and financial problem were the important reasons for the relatively low daily dose administered (28 mg). With combined application of carvedilol and amiodarone there was one hypotension, that required carvedilol withdrawal. In two patients the small doses of carvedilol were tolerated despite the chronic obstructive lung disease. Not a single patient experienced the increase in urea and creatinin following carvedilol introduction.

Among the first congestive heart failure patients in the country, patient B.S. started with carvedilol in March, 1996. He has left ventricle end-diastolic diameter 80 mm and ejection fraction 30%, when carvedilol therapy started. Also, he used to have over 20 attacks of non-sustained ventricular tachycardia per day, resulting in presyncopal crises. Following amiodarone and carvedilol therapy (together with ACE inhibitor, diuretic, etc), Holter documented no ventricular tachycardia. His left ventricle diameters and ejection fraction remained unchanged for the next five years. He used to work his job almost until fatal ventricular fibrillation together with staphylococcus aureus pneumonia occurred in 2001.

Eleven patients died. Four patients died in cardiogenic shock with pulmonary edema, four from acute myocardial reinfarction and three of presumably ventricular fibrillation. Amiodarone and carvedilol might be contributory factors presumably due to proarrhythmia, but this is very difficult to evaluate. The potentially lethal severe bradycardia might be directly attributed to combination of amiodarone and carvedilol, but it was not recorded, due in part to very careful dose titration. One patient had the moderate bradycardia (48 bpm). The haemorrhage due to excessive INR increase (which is not rare with amiodarone and the oral anticoagulants) may contribute to death, too, especially in old patients with the comorbidity.

In 9 patients there was also mild hypothyroidism induced, that resolved with drug withdrawal.

First degree AV block (without progression to second and third) was found in 16 patients. This is not more than in our patients treated with amiodarone in the similar doses (without carvedilol). The following explanations are likely: 1) we decreased amiodarone when we increased carvedilol; 2) the drugs do not interact so pronouncedly in the doses applied; 3) the regular controls

prevented some adverse effects from being worse; 4) we have only the limited number of patients and much larger studies are needed. Larger, double - blind trial with amiodarone vs placebo evaluation upon the hospitalization duration as well as the time to carvedilol initialization, the rate of the rehospitalizations and of the mortality is needed. Nevertheless, the first experience is clearly favorable and encouraging.

Also, there were 34 QTc prolongation without torsade de pointes, due to amiodarone itself.

The difficulties with maintaining INR in the therapeutic range with amiodarone + carvedilol were the same as with amiodarone alone. Not a single patient with the amiodarone - induced pulmonary fibrosis was observed.

Discussion

"Heart failure is a mortal illness, more serious than most malignancies" (28). Thus, the heart failure is sometimes called "the cancer of the heart" (35). The another reason to study the congestive heart failure is the rising incidence and prevalence of this morbid and dangerous condition. For example, for the people 45-55 years of age, congestive heart failure *incidence* is 1%-2% per year; for elderly patients (older than 85 years), over 1 in 10 will develop congestive heart failure each year (36).

Also, cardiovascular disease is the leading cause of death in the developed world today, and the congestive heart failure is the only cardiovascular disease that is actually increasing in both incidence and prevalence (36).

There have been the suggestions that slowing the heart rate in congestive heart failure may improve the prognosis (1, 2). This seems logical if we have in mind that the heart pumps about 7 tons daily (in healthy persons: minute volume $5L \times 1440$ minutes per day = 7200 kg/ 24 hours). By reducing the heart rate for approximately 15-20% we might unload the heart for a 1000 kg /24 hours.

In the medical literature *the significance of tachycardia has been increasingly recognized* (1). Tachycardia has worse influence in patients with the coronary artery disease as a ground cause of the congestive heart failure, which is now the typical situation (36). Namely, tachycardia in the congestive heart failure worsens *both congestive heart failure* per se (by decreasing left ventricle filling time, and left ventricle filling is already impaired by elevated left ventricular pressure) *and coronary artery disease* by itself (by the tachycardia -induced increase in the oxygen consumption, as well as the tachycardia - induced decrease in the oxygen supply, due to the decreased diastole duration). The resulting ischemia causes the additional abnormalities in both systolic and diastolic heart functions, ventricular arrhythmias, pain (which further elevates blood catecholamines and worsens both coronary artery disease and congestive heart failure), etc. In this way the vicious cycle arises, as Kasper (28) wrote: "Summary of congestive heart failure - the vicious cycle".

Our observation confirms that ischemia is very common in pulmonary edema (37). It has etiologic and therapeutic significance, being also the useful marker of the worse inhospital prognosis (37).

Amiodarone may decrease the incidence of sudden cardiac death (presumably arrhythmic) in the congestive heart failure /post acute myocardial infarction patients (1, 2, 20, 38, 39). This effect is believed to be pronounced in the patients with congestive heart failure and higher heart rate.

The similar mechanism might be suggested also for carvedilol, which improves survival in the congestive heart failure, too. In patients treated long-term after an acute myocardial infarction complicated by left-ventricular systolic dysfunction, carvedilol reduced the frequency of all-cause and cardiovascular mortality, and recurrent, non-fatal myocardial infarctions. These beneficial effects are additional to those of evidence-based treatments for acute myocardial infarction including ACE inhibitors (40).

Carvedilol is beta (and alfa) blocker and decreases the deleterious effects of neurohormonal activation in the congestive heart failure (41). In addition, it protects from the direct toxicity of the norepinephrine. Carvedilol also lowered the plasma levels of angiotensin II and aldosterone (42). The anti-oxidant activity of carvedilol is relevant for the maintenance of myocardium viability (43). The congestive heart failure is the condition with the oxidative stress (44).

In the patients with atrial fibrillation complicating congestive heart failure, carvedilol significantly improves the left ventricular ejection fraction (45).

Carvedilol improves the left ventricle diastolic function and diminishes mitral regurgitation (46).

Following actions of beta blockers may be useful, too, as suggested by Deedwania (7): "Mechanisms of sudden death reduction by beta blockade in congestive heart failure: heart rate slowing, prevention of catecholamine-induced myocyte toxicity/apoptosis, antiarrhythmic effects, antifibrillatory actions, anti-ischemic effects, up-regulation of beta-receptor sensitivity and decreased sympathetic outflow."

With beta blockers in the congestive heart failure patients, starting with the minimum possible dose and titrating upward, monitoring closely, we may see an increase in left ventricular ejection fraction and a decrease in ventricular volumes - what has been called "*reverse remodeling*", where the ventricle actually gets smaller and more cylindrical again. Together with this change in ejection fraction, there is an accompanying decrease in mortality. This is the lesson of the carvedilol trials (28).

This is important since left ventricle remodeling has been shown to possess direct effects on both arrhythmias (through pressure-sensitive potassium channels) and on pump failure (and death), both mediated through overactivation of the various sympathetic neurohormonal systems, leading to the vasoconstriction and the increased preload, as well as endothelial dysfunction and sodium retention (28).

Heart failure patients with the lowest left ventricular ejection fraction or the highest heart rate at baseline had the greatest gain in ejection fraction after treatment with carvedilol (47).

Having in mind that 40%-60% of patients with the left ventricle systolic dysfunction will die suddenly (28), it seems very logical to use antifibrillatory agent amiodarone in combination with carvedilol, which has beta blocking activity including antifibrillatory one (3). The beneficial interaction is between amiodarone and beta blockers. The combination of amiodarone and beta-blockers appears superior to amiodarone alone in the prevention of sudden death (4). Impressive amelioration of clinical (NYHA class) and echocardiographic parameters occurs in heart failure patients treated with amiodarone and carvedilol (48).

By synergic actions, amiodarone and beta blockers may increase the potential for prolonging survival in certain subsets of patients without necessarily producing undue bradycardia or heart block. This has been documented in a number of recent observations (20).

Amiodarone without carvedilol has been very useful in short-term therapy of severe congestive heart failure and / or unstable coronary artery disease (23, 49). It is the drug of choice for conversion of paroxysmal / persistent atrial fibrillation in patients with congestive heart failure (50, 51). Amiodarone solved the problem of excessive tachycardia in our severe congestive heart failure patients, without clinically important side-effects (except one bradycardia and frequent INR prolongations).

Amiodarone and carvedilol combination has been well-tolerated over years (with precise control of possible side effects of amiodarone). Amiodarone should stay in therapy if atrial fibrillation / ventricular tachycardia / sinus tachycardia persists despite maximal doses of carvedilol, that patient tolerates. Amiodarone was shown not to increase side effects of carvedilol (52).

Such combination (amiodarone + beta-blockade) produced a greater reduction in the incidence of atrial fibrillation after coronary artery bypass surgery and a stronger trend toward reduction in the duration of arrhythmia and length of stay (53).

In the EMIAT and CAMIAT trials it was also shown that concomitant treatment with amiodarone and a beta-blocker is far more effective than either agent given alone, suggesting possible synergistic effects of these drugs in high-risk patients (7).

Our approach concerning amiodarone and carvedilol for patients with both severe congestive heart failure and sinus rhythm is essentially the following one:

- 1) to administer amiodarone (provided there is no contraindication) to slow the heart rate, to pre-

vent / treat ventricular tachycardia and to prevent atrial fibrillation;

- 2) following clinical stabilization to include carvedilol, "overlapping" it with amiodarone;
- 3) to exclude amiodarone as soon as possible (because of its potentially dangerous unwanted effects) if and when patient's situation allows it, and
- 4) to introduce amiodarone again if serious ventricular arrhythmias recur and/or atrial fibrillation occurs and/or heart rate control becomes suboptimal.

We believe that amiodarone is the single drug that can be reasonably safely administered to the patients with such excessive sinus tachycardia in order to reach the clinical stability, sufficient to allow us to introduce carvedilol. The risk associated with pronounced tachycardia (f.e. 130 bpm) is particularly evident in patients with ischaemia. It might be not wise to wait for the heart rate to get reduced with digitalis as the only drug with negative chronotropic action in therapy.

Conclusion

- 1) There is the rationale to combine amiodarone and the beta blocker in selected patients with severe congestive heart failure and sinus tachycardia, because drugs act synergistically to decrease the heart rate, prevent atrial fibrillation and ventricular dysrhythmias, and may prolong life.
- 2) In the absence of contraindications, amiodarone can be given immediately, and carvedilol following the resolution of decompensation, which can be achieved within 10 days in most patients.
- 3) At the present time evidences suggest carvedilol (among drugs with beta blocker capabilities) for congestive heart failure patients, because it offers both beta and alfa blockade, and antioxidative properties.
- 4) The combination of amiodarone and carvedilol was safe and efficacious in our congestive heart failure patients with sinus tachycardia, in the observational study which started in March 1996.
- 5) The control of congestive heart failure becomes better due to reverse remodeling of the left ventricle, as well as by improved course of coronary artery disease (one of the most important causes of the congestive heart failure), due to the heart rate reduction (and thus of the myocardial oxygen demand) and improvement in the coronary artery flow due to the increased duration of diastole.
- 6) Nevertheless, frequent control examinations should be undertaken, to diminish the risk of unwanted effects of this combination.

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SEDMOGODIŠNJA PRIMENA KARVEDILOLA I AMIODARONA U TEŠKOJ INSUFICIJENCIJI SRCA SA SINUSNOM TAHIKARDIJOM: OBRAZLOŽENJE I BEZBEDNOST

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Kratak sadržaj: Cilj rada je da pruži obrazloženje za kombinaciju amiodarona i karvedilola u teškoj srčanoj insuficijenciji sa sinusnom tahikardijom, jer o tome ima vrlo malo izveštaja u raspoloživoj medicinskoj literaturi. Analizovano je 112 bolesnika sa sinusnom tahikardijom i srčanom insuficijencijom (NYHA III-IV), 74 sa koronarnom bolešću, 59 muškaraca i 53 žene, 64 ± 9 god, od marta 1996.

Rezultati: amiodaronom sublingvalno ili intravenski smo smanjili SF sa 130,2 ± 4,9 na 94,0 ± 7,4 /min. (P<0,0001) za 2 dana. Dodatkom karvedilola po rekompensaciji je srčana frekvenca nakon 5-10 dana dodatno redukovana sa 94,0 ± 7,4 /min. na 81,0 ± 3,6 /min. (P<0,0001). Očigledno je smanjen broj rehospitalizacija. Našem prvom pacijentu su enddiastolni dijametar leve komore = 80 mm i ejekciona frakcija = 30% ostali nepromenjeni 5 godina. Nuzefekti: blag hipotireoidizam (9 pacijenta), AV blok I^o (16), produženje QTc bez torzade (34) i otežana kontrola INR-a (32 pacijenta).

Zaključci: 1) Kombinacija amiodarona i karvedilola u teškoj SI, u sinusnoj tahikardiji je opravdana - da se smanji opterećenje srca frekvencom, a time i ishemija, da se produži diastola, a time i punjenje kako leve komore, tako i koronarnih arterija, sa smanjenjem ishemije i reverznim remodelovanjem, te da se preveniraju / bolje kontrolišu atrijalna fibrilacija i ventrikularna tahikardija. 2) Amiodaronom se ubrzava rekompensacija, a onda uvodi karvedilol. 3) Bezbednost kombinacije je vrlo prihvatljiva u odnosu na korist.

Ključne reči: Amiodaron, karvedilol, kongestivna srčana insuficijencija, sinusna tahikardija