DOI: 10.2298/SARH1302029G
UDC: 616.12-008.46-085.22

Effects of Combination of AT_1-Antagonist Candesartan Cilexetil and ACE-Inhibitors in Patients with Congestive Heart Failure

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SUMMARY

Introduction Combination of ACE-inhibitors with angiotensin-II type 1 receptor antagonists could provide better blockade of RAAS system compared with monotherapy.

Objective The aim of this study was to evaluate hemodynamic and neurohumoral effects at rest and during exercise of Candesartan cilexetil as add-on therapy to ACE-inhibitors in patients with heart failure NYHA class III to IV.

Methods This was a prospective, randomized, double-blind, placebo-controlled, parallel group study. Thirty-five patients received either Candesartan 8 mg/16 mg (1st and 2nd week/ of 3-24) or placebo as add-on therapy to their previous ACE-inhibitor during a 24-weeks treatment period.

Results Peak aerobic capacity remained constant in the Candesartan group of patients (0.06±1.43 mL/min/kg) and slightly decreased in the placebo group (-1.10±1.51 mL/min/kg), without a statistically significant difference between the groups (p=0.13). Exercise time showed a relevant increase in the Candesartan (31.9±58.5 sec) and a significant decrease in the placebo group (-25.9±85.9 sec) compared to baseline value. The difference between the studied groups was statistically significant (p<0.001). Relevant differences between the two groups were observed in the changes of right atrial pressure at rest (Candesartan: -1.9±1.7 mmHg, placebo: 1.0±2.7 mmHg, p<0.01), pulmonary capillary wedge pressure at rest (Candesartan: -3.1±3.8 mmHg, placebo: 0.2±4.6 mmHg, p<0.05) and systemic vascular resistance at maximum exercise (Candesartan: -141.9±253.3 dyne*sec/cm^5, placebo: 47.3±221.0 dyne*sec/cm^5, p<0.05).

Conclusion The efficacy of CHF treatment of congestive heart failure was moderately improved by Candesartan as add-on therapy to ACE-inhibitors.

Keywords: Candesartan cilexetil; angiotensin receptor blockers; ACE-inhibitors; congestive heart failure

INTRODUCTION

Activation of the renin-angiotensin-aldosterone-system (RAAS) is a critically important determinant in the pathophysiological processes that lead to the progression of heart failure and sudden death. Angiotensin-II, acting at the AT_1 receptor, leads to vasoconstriction, norepinephrine release, aldosterone secretion, vascular hypertrophy and remodeling and also stimulates the synthesis and the release of the extremely potent vasoconstrictor peptide endothelin-1 from endothelial cells [1, 2].

ACE-inhibitors have been demonstrated to increase survival in congestive heart failure (CHF), primarily by reducing the rate of progression of left ventricular dilatation and decompensation. However, ACE-inhibitors do not block the formation of A-II completely. Vasoconstriction is with blocking AT_1-receptors more decreased. At the same time, through binding A-II for AT_2-receptors an additional vasodilatory effect has been observed. Thus, the combination of ACE-inhibitors and A-II antagonists offers the theoretical advantage of increasing bradykinin through blocking the actions of A-II and may result in a synergistic effect [1, 2, 3].

Candesartan is a highly potent and long acting AT_1-receptor antagonist. In Germany it was launched for the treatment of essential hypertension in 1997. In 2004 Candesartan was established for the treatment of CHF in patients with reduced left ventricular systolic function.

A few major studies confirm efficacy and safety of Candesartan in the treatment of chronic heart failure. Candesartan proved to be well tolerated at the maximum dose of 32 mg once daily in the majority of patients with CHF already on regimen including ACE-inhibitors [4, 5].

A study of the effects of Candesartan alone, Enalapril alone and in combination in 768 patients with CHF demonstrated that Candesartan alone was as effective, safe and tolerated as Enalapril in this patient population. The combination of Candesartan and Enalapril was more beneficial in preventing left ventricular remodeling than either Candesartan or Enalapril alone [6].

In the large CHARM trial Candesartan was evaluated in heart failure assessment of reduction in mortality and morbidity programs. Overall, 7,599 patients with CHF were assigned to one of three protocols: the CHARM-Alternative, for patients with ACE-inhibitor

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intolerance; the CHARM-Added, for patients established on ACE-inhibitor therapy; and the CHARM-Preserved, for patients with isolated diastolic dysfunction. The primary outcome for the overall analysis was all-cause death, while each individual protocol's primary outcome was occurrence of cardiovascular death or unplanned hospital admission for heart failure (HF). According to main conclusions of the study, Candesartan significantly lowers cardiovascular mortality, overall mortality and HF hospitalizations in patients with LV systolic dysfunction. It is an appropriate alternative to ACE-inhibitor intolerant patients or to appropriately selected patients on established ACE-inhibitor therapy [7-10].

OBJECTIVE

The study objective was to answer the question whether Candesartan as add-on therapy to ACE-inhibitors (and according to patients pre-medication also an addition to digitalis and/or diuretics) improves exercise capacity (VO_2 max) in patients with symptomatic heart failure NYHA class III to IV with EF<35% over a treatment period of 24 weeks.

Secondary objectives of the study were to determine whether treatment with Candesartan improves hemodynamics during exercise and at rest, symptoms and signs, left ventricular systolic and diastolic function and neurohormone levels.

METHODS

This was a prospective, randomized, double-blind, parallel group study with two treatment arms. The study comprised a 2-weeks run-in period and a 24-weeks treatment period. During the study all patients continued to take their previous ACE-inhibitor. During the treatment period the patients received either Candesartan or placebo as add-on therapy. The treatment period started with intake of Candesartan 8 mg or placebo for 2 weeks. Thereafter, the dosage was doubled and patients took Candesartan 16 mg or placebo for another 22 weeks. Candesartan 8 mg tablets and placebo tablets of identical appearance were used in both phases of the treatment period.

The following doses were regarded as minimum doses for ACE-inhibitors: Captopril 50 mg, Enalapril 10 mg, Lisinopril 5 mg, Perindopril 4 mg, Ramipril 5 mg. The study medication (ACE-inhibitor and Candesartan or placebo) was taken orally every morning before breakfast. Baseline treatment with digitalis, diuretics, beta blockers, class-III-antiarrhythmics (amiodarone, sotalol) was continued during the study.

The study was performed in outpatients of the Kerckhoff-Klinik Bad Nauheim, Germany. Male and female patients ≥18 years of age with moderate to severe symptomatic heart failure (NYHA class III to IV) were enrolled. Patients were eligible for inclusion if they had impaired left ventricular function (ejection fraction <35%), if they were on stable ACE-inhibitor therapy for at least one month prior to inclusion and if they were suitable for add-on therapy with AT_1-receptor antagonists.

The patients returned to the study centre at the start of the run-in period (Visit 1), at the start of the treatment period (Visit 2), at 2, 4, 8 and 16 weeks after the start of the treatment period (Visits 3, 4, 5 and 6) and at the end of the treatment period (Visit 7). The following investigations were performed at the visits to the study centre: ergospirometry during symptom-limited bicycle ergometry, right heart catheterization during symptom-limited bicycle ergometry, echocardiography, self-assessment of dyspnea, self-assessment of quality of life (Visits 2 and 7).

Primary efficacy parameter was the change in VO_2 max from Visit 2 to Visit 7. Changes in the other cardiologic variables were regarded as secondary efficacy parameters. The primary efficacy parameter was analyzed for superiority of Candesartan vs. placebo as add-on therapy to an ACE-inhibitor. The secondary efficacy parameters were analyzed for differences between treatment groups.

To this, an analysis of covariance (ANCOVA) was performed using treatment and enrolment period as factors and the baseline value (Visit 2) as covariate. Candesartan was considered as superior to placebo regarding the change in VO_2 max from Visit 2 to Visit 7 if the test for LS-mean difference <0 yielded a $p \leq 0.025$. Differences in secondary efficacy parameters between treatment groups were concluded if the corresponding test for LS-mean difference = 0 yielded a $p \leq 0.05$.

The study was approved by the Independent Ethics Committee (IEC – LÄK Hessen, Frankfurt, Germany).

RESULTS

Disposition

In total 35 patients were enrolled in the study. Eighteen patients were randomized to Candesartan cilexetil and 17 patients were randomized to placebo as add-on therapy to their ACE-inhibitor. All patients received study medication at least once and were included in the safety analysis. Six patients were excluded from the intention-to-treat (ITT) analysis because no valid ergospirometry was performed at Visit 2 and/or at Visit 7. Thus, the ITT population comprised 29 patients, 14 patients in the Candesartan and 15 patients in the placebo group.

Protocol deviations

All protocol deviations were regarded as minor in all patients except three. Discontinuation of concomitant intake of a diuretic at Visit 5 was regarded as a major protocol deviation. Minor protocol deviations were primarily made up by deviations from the time schedule. No patient violated any of the in- or exclusion criteria at screening.

doi: 10.2298/SARH1302029G

Demographic and baseline characteristics

Patients in both treatment groups were predominantly of male sex. Patients in the placebo group were slightly older than patients in the Candesartan group. Body weight was higher in the Candesartan group but no relevant difference between groups was observed in body height. Systolic and diastolic blood pressure was higher in the placebo group, whereas pulse rate was higher in the Candesartan group (Table 1).

Baseline values of all efficacy parameters were within expected ranges for patients suffering from CHF (NYHA class III to IV). Most parameters did not show any differences in baseline values between treatment groups. In the following, parameters with remarkable differences at baseline are mentioned (mean±SD). During bicycle ergometry, systolic blood pressure at rest and systemic vascular resistance at rest were higher in the placebo group, whereas heart rate at rest was higher in the Candesartan group (Table 2).

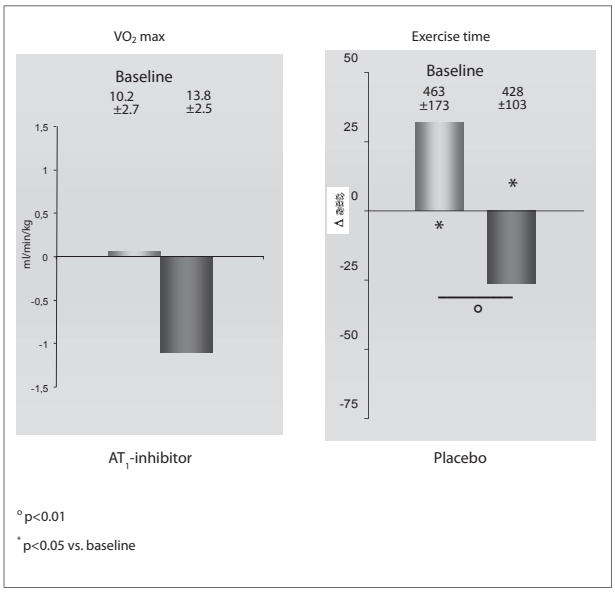
Table 1. Clinical and hemodynamic characteristics at baseline

Parameter	Candesartan group (n=18)	Placebo group (n=17)
Male (n)	15	14
Female (n)	3	3
Age (years)	52.7±9.5	55.6±13.6
Body weight (kg)	97.7±15.4	85.7±15.7
Body height (cm)	176.9±6.6	172.1±10.2
Pulse rate (min^{-1})	78.2±11.5	69.0±12.0
Systolic blood pressure (mm Hg)	124.6±23.5	136.4±19.4
Diastolic blood pressure (mm Hg)	86.3±10.6	84.2±12.4
Systemic vascular resistance (dyne*sec/cm^5)	1454.9±306.3	1698.2±491.9
LVEF (%)	21.4±6.0	25.4±4.8
Peak VO_2 (ml/min/kg)	10.2±2.7	13.8±2.5
PCWP (mmHg)	13.5±4.2	14.5±7.3
CO (l/min)	5.1±0.9	4.3±0.7

n – number of patients

Table 2. Concomitant medication at baseline – number of patients

Parameter	Candesartan group (n=18)	Placebo group (n=17)
Beta blockers	18	17
ACE inhibitors	18	17
Loop diuretics	16	15
Aldosterone antagonists	10	10
Cardiac glycosides	11	9
Antithrombotic agents	13	15
Serum lipid reducing agents	6	8



Graph 1. Change in oxygen uptake and bicycle exercise time after 24 weeks

Efficacy results

Primary efficacy parameter

The primary efficacy variable at baseline, VO_2 max, was significantly lower (p<0.001) in the Candesartan (10.2±2.7 mL/min/kg) than in the placebo group (13.8±2.5 mL/min/kg).

From Visit 2 to Visit 7, VO_2 max remained about constant in the Candesartan group (0.06±1.43 mL/min/kg) and slightly decreased in the placebo group (-1.10±1.51 mL/min/kg) (Graph 1).

VO_2 max was not significantly improved by Candesartan or placebo and Candesartan showed no significant effect on VO_2 max in comparison with placebo (p=0.13).

Secondary efficacy parameters

Ergospirometry

Graph 1 provides an overview of the changes in ergospirometry results from Visit 2 to Visit 7. These results indicated a tendency to a decrease in oxygen uptake at rest in the Candesartan but not in the placebo group, whereas no change in oxygen pulse at rest and oxygen pulse at maximum exercise were observed in both treatment groups (p>0.05).

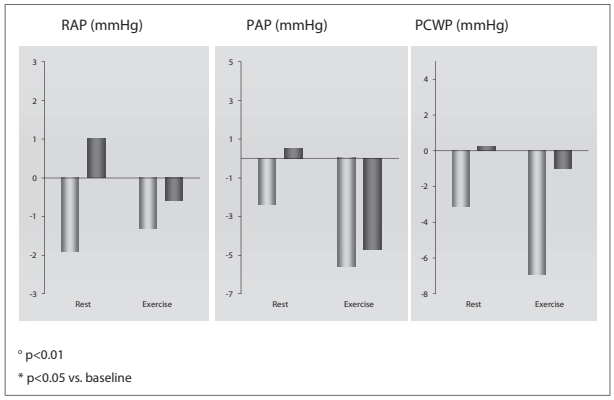
Bicycle ergometry and right heart catheterization

Changes in routine bicycle ergometry and right heart catheter results from Visit 2 to Visit 7 are presented in Graphs 2 and 3. During bicycle ergometry, patients in the Candesartan group showed a relevant increase in exercise time (31.9±58.5 sec) (p=0.01), whereas a relevant decrease was observed in the placebo group (-25.9±85.9 sec) compared to baseline value (p<0.05). The difference between treatment groups was significant (p<0.001).

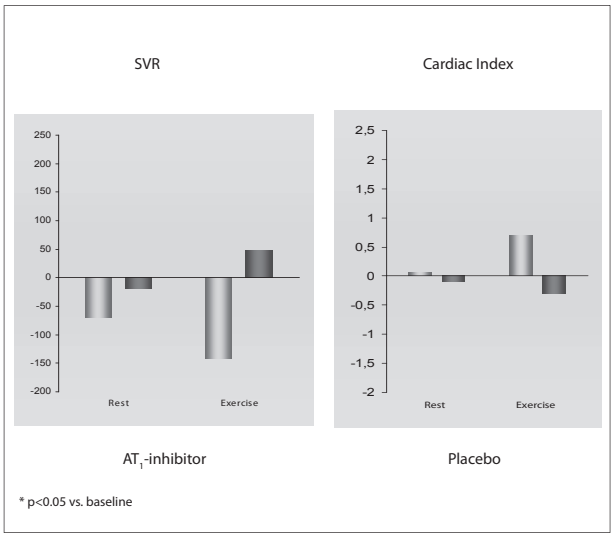
Relevant reductions in pulmonary capillary wedge pressure were observed both at rest and at maximum exercise ($p<0.01$). Relevant reductions in systemic vascular resistance and mean pulmonary artery pressure occurred at maximum exercise ($p<0.05$), as seen on Graphs 2 and 3. Furthermore, heart rate and mean pulmonary artery pressure at rest tended to decrease and cardiac index at maximum exercise tended to increase in the Candesartan group, as seen on Graphs 2 and 3.

Except for a relevant decrease in mean pulmonary artery pressure at maximum exercise ($p<0.05$), none of these changes was observed in the placebo group. However, only patients in the placebo group showed relevant reductions in diastolic and mean arterial blood pressure at maximum exercise ($p<0.01$).

Finally, relevant differences between treatment groups were observed in changes of right atrial pressure at rest (Candesartan: -1.9±1.7 mmHg, placebo: 1.0±2.7 mmHg, $p<0.01$), pulmonary capillary wedge pressure at rest (Candesartan: -3.1±3.8 mmHg, placebo: 0.2±4.6 mmHg, $p<0.05$) and systemic vascular resistance at maximum exercise (Candesartan: -141.9±253.3 dyne*sec/cm^5, placebo: 47.3±221.0 dyne*sec/cm^5, $p<0.05$) (Graphs 2 and 3).



Graph 2. Change in right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) after 24 weeks



Graph 3. Change in systemic vascular resistance (SVR) and cardiac index after 24 weeks

Dyspnoea and quality of life

On a 100 mm visual analogue scale (VAS) no relevant difference in the reduction of dyspnea between Candesartan and placebo treated patients was observed.

There was no relevant change in any dimension of health-related quality of life in both treatment groups, except for a relevant increase in vitality in the placebo group. However, vitality assessments were lower in placebo than in Candesartan treated patients at Visit 2, and the increase in vitality in the placebo group mostly compensated for this difference. Health-related quality of life was assessed with the SF-36 questionnaire.

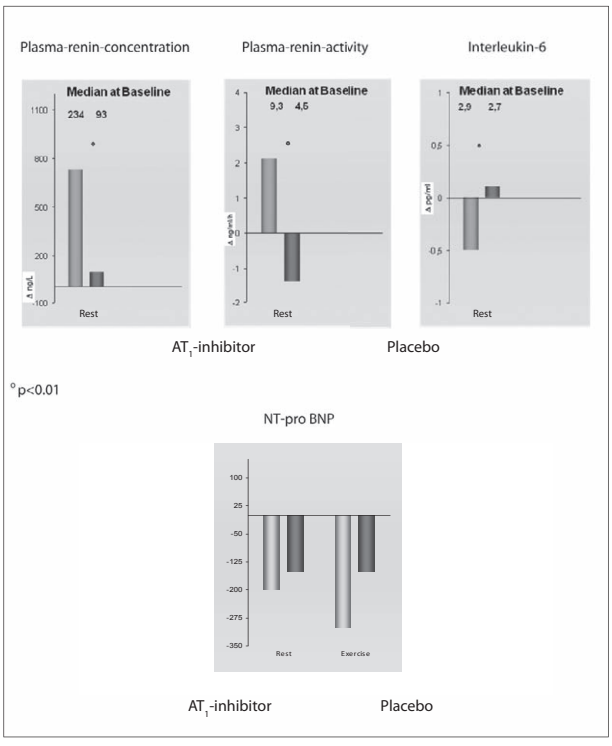
Echocardiography

The echocardiography parameters did not show any statistically relevant changes in both investigated groups. However, a tendency to an increase in the left ventricular ejection fraction was observed in both treatment groups, but that was not relevant ($p>0.05$).

Hormone levels

Graph 4 provides an overview of the changes in hormone levels from Visit 2 to Visit 6.

Plasma-renin-concentration was significantly increased in the group with Candesartan (279.5±901.9 ng/L, $p<0.01$), but in the placebo group it remained unchanged (-29.0±211.9 ng/L, $p>0.05$). Furthermore, the Candesartan group patients showed a relevant decrease in Interleukin



Graph 4. Change in plasma renin concentration, plasma renin activity, NT-proBNP and interleukin-6 after 24 weeks

doi: 10.2298/SARH1302029G

6 concentration ($p<0.05$) and a tendency to a decrease in NT-proBNP at rest ($p=0.06$) (Graph 4). Only the change in pooled data of plasma-renin-activity and plasma-renin-concentration at rest showed relevant differences between the Candesartan and placebo group ($p<0.05$) (Graph 4).

DISCUSSION

In the previous non-invasive study in patients with congestive heart failure, treatment with Candesartan demonstrated significant improvements in exercise-tolerance, cardio-thoracic ratio as well as symptoms and signs of heart failure and was overall well tolerated [5]. Referring to VO2 max, our study failed to show superiority of Candesartan compared to placebo as add-on therapy to ACE-inhibitors for the treatment of CHF. An explanation could be in a relatively small number of included patients compared to predicted studies with Candesartan. However, patients in the Candesartan group showed a relevant increase in exercise time, whereas a relevant decrease was observed in the placebo group. According to Narang et al. [11], exercise time is an even better variable for the assessment of therapeutic interventions in patients with CHF than oxygen consumption. Thus, the increase in exercise time can be interpreted as a clear indication of an improvement of CHF treatment by co-administration of Candesartan to ACE-inhibitors.

Other parameters of cardiac function have to be examined separately for resting and for working conditions. At rest, cardiac function was improved by a reduction of cardiac work for about the same time of blood delivered. Cardiac work was primarily reduced by reduction of systemic vascular resistance and venous pooling. During right heart catheterization and bicycle ergometry, this appeared as decrease in blood pressure, as well as decrease in right atrial pressure, pulmonary capillary wedge pressure and mean pulmonary artery pressure. According to Mitrović et al. [12], after 3 months mean PCWP values in all treatment groups (2, 4, 8 and 16 mg Candesartan) were considerably lower as compared with corresponding single-dose values. For all time points, the lowest and statistically significant mean PCWP values as well as mean PAP values were obtained in the Candesartan 16 mg group. The study followed hemodynamic and neurohormonal effects of Candesartan in patients with CHF and confirmed dose-dependent, significant reductions of PCWP in doses 8 and 16 mg versus placebo [12]. In the study with Valsartan in patients with mild to moderate CHF after 2 months of treatment mean PCWP values were decreased, but not significant compared to placebo [13]. At maximum exercise, in our investigation Candesartan enhanced the physiological reduction of systemic vascular resistance. It also seems to be the result in previous studies [12, 13]. The reduction of cardiac output at rest and the enhancement of the physiological reduction of systemic vascular resistance allowed for an increase in the amount of blood delivered at maximum exercise. During right heart catheterization and bicycle ergometry, this appeared as an increase in cardiac index. Decrease of blood pressure was compensated by the increase in cardiac output that finally caused the increase in exercise time. The reduction of right and left ventricular filling pressures was observed at maximum exercise. Such changes in the hemodynamic parameters of cardiac function suggest an improvement of CHF treatment by co-administration of Candesartan to ACE-inhibitors.

As can be expected, as a result of effective RAAS blockade, plasma-renin-concentration and plasma-renin-activity were compensatory significantly increased in the group with Candesartan. Results of the long-lasting Framingham Heart Study suggest that increase of plasma-renin-concentration has no significant influence on cardiovascular events [14]. At the same time, permanent and dose-dependent decrease in aldosterone and atrial natriuretic factor were also registered in our and previous studies with Candesartan in patients with CHF. This can be considered as the positive hemodynamic effect of Candesartan in this population of patients [12, 13].

Although the improvement in cardiac function was observed, our patients with congestive heart failure had no significant change either in the quality of life or reduced symptoms like dyspnea, despite improved quality-of-life results observed by other investigations with more patients [4, 5, 12, 13]. A slight decrease in NT-proBNP at rest as well as at maximum exercise was also registered. It could be possible that the period of 16 weeks was too short for the registration of Candesartan effects on dyspnea and other symptoms of heart failure, so that the period of time could be extended in further clinical studies of Candesartan.

CONCLUSION

Combination of AT_1-inhibitor Candesartan and ACE-inhibitor in patients with moderate to severe symptomatic congestive heart failure showed a relevant increase in exercise time and relevant decrease in values of right atrial pressure, pulmonary capillary wedge pressure at rest and systemic vascular resistance at maximum exercise.

No significant change in exercise capacity (VO_2 max) was observed.

Our results suggest moderate positive additional therapy effects of Candesartan as add-on therapy to ACE-inhibitors in the treatment of congestive heart failure.

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Ефекти примене комбинације антагонисте AT_1-рецептора кандесартан-цилексетила и *ACE*-инхибитора код болесника с конгестивном инсуфицијенцијом срца

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КРАТАК САДРЖАЈ

Увод Комбинација *ACE*-инхибитора и блокатора ангиотензинских рецептора може обезбедити бољу блокаду система РААС у поређењу с монотерапијом.

Циљ рада Циљ рада је био да се утврде хемодинамски и неурохуморални ефекти кандесартан-цилексетила у стању мировања и при напору у оквиру додатне терапије *ACE*-инхибиторима код болесника с инсуфицијенцијом срца *NYHA* класе *III* и *IV*.

Методе рада Студија је била проспективна, рандомизирана, дупло слепа, плацебо контролисана, са паралелним групама. Укупно 35 болесника примило је кандесартан у дози од 8 *mg* прве и друге недеље, односно 16 *mg* од треће до 24. недеље, или плацебо током 24 недеље у оквиру додатне терапије *ACE*-инхибитором који су раније користили у терапији.

Резултати Аеробни капацитет је остао непромењен код испитаника који су примали кандесартан (0,06±1,43 *ml/min/kg*), а био је благо снижен у групи која је примала плацебо (-1,10±1,51 *ml/min/kg*), без статистички значајне разлике међу групама (p=0,13). У поређењу с почетним вредностима, време приликом напора се значајно повећало у групи испитаника који су примали кандесартан (31,9±58,5 *s*), док се код болесника који су примали плацебо значајно смањило (-25,9±85,9 *s*). Разлика између испитиваних група била је статистички значајна (p<0,001). Значајне разлике међу испитиваним групама забележене су и у променама вредности притиска десне преткоморе у стању мировања (кандесартан: -1,9±1,7 *mm Hg*; плацебо: 1,0±2,7 *mm Hg*; p<0,01), плућног капиларног притиска у стању мировања (кандесартан: -3,1±3,8 *mm Hg*; плацебо: 0,2±4,6 *mm Hg*; p<0,05) и системског васкуларног отпора при максималном напору (кандесартан: -141,9±253,3 *dyne·s/cm*^{5}; плацебо: 47,3±221,0 *dyne·s/cm*^{5}; p<0,05).

Закључак Ефикасност лечења болесника с инсуфицијенцијом срца било је благо побољшано додавањем кандесартана *ACE*-инхибиторима.

Кључне речи: кандесартан-цилексетил; блокатори ангиотензинских рецептора; *ACE*-инхибитори; конгестивна инсуфицијенција срца

Примљен • Received: 17/10/2011 **Прихваћен • Accepted:** 26/06/2012