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Effect of candesartan treatment on echocardiographic indices of cardiac remodeling in post-myocardial infarction patients

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SUMMARY

Objective: Myocardial infarction has unfavorable effect on structural and functional properties of the myocardium, referred to as cardiac remodeling. Left ventricular mass, left ventricular mass index, and relative wall thickness are important predictors of cardiac remodeling. In this study, we investigated the effect of candesartan treatment in comparison with zofenopril treatment on echocardiographic indices of cardiac remodeling in post myocardial infarction patients.

Material and Methods: In this prospective study, patients who underwent successful percutaneous coronary intervention were randomly assigned to a candesartan or zofenopril treatment. After randomization, echocardiographic indices of cardiac remodeling including left ventricular mass, left ventricular mass index, and relative wall thickness were evaluated before the start of treatment along with 1- and 6-month follow-ups.

Results: According to our study, candesartan group showed significant reduction of estimated left ventricular mass and left ventricular mass index at 6-month follow-up visit compared to baseline values (199.53±38.51 g vs. 212.69±40.82 g; 99.05 g/m^2 (90.00–116.5) vs. 106.0 g/m^2 (96.0~123.00), p<0.05, respectively). This trend was also observed in zofenopril group during the 6-month period (201.22±40.07 g vs. 207.52±41.61 g; 101.0 g/m^2 (92.25–111.75.0) vs. 104.50 g/m^2 (95.0~116.75), p<0.05, respectively). Although both classes of drugs had favorable effects on post-myocardial infarction cardiac remodeling, the absolute benefit was more prominent in candesartan group as compared to zofenopril group (p<0.05).

Conclusion: Our results suggest that candesartan treatment following myocardial infarction may potentially be useful in terms of improving post-myocardial infarction cardiac remodeling.

Keywords: Myocardial infarction. Cardiac remodeling. Candesartan treatment.

INTRODUCTION

Myocardial infarction (MI) has unfavorable effect on structural and functional properties of the myocardium, referred to as cardiac remodeling. This pathological condition is associated with deterioration in ventricular performance and adverse cardiac events, including heart failure and ventricular arrhythmias[1]. Despite significant improvements in coronary interventions, coronary care, and novel medical therapies, patients presenting MI still develop ventricular dysfunction in the chronic stage of the disease as a result of cardiac remodeling[2].

Left ventricular (LV) mass, LV mass index (LVMI), and relative wall thickness (RWT) are important predictors of cardiac remodeling and are associated with cardiovascular morbidity and mortality. It has been observed that these geometrical indices may provide considerable benefits for assessment of different patterns of cardiac remodeling, such as concentric remodeling, concentric hypertrophy, and eccentric LV hypertrophy[3,4].

According to previous studies, angiotensin II type 1 receptor blockers (ARBs) may reverse cardiac hypertrophy and structural remodeling and reduce the risk of ventricular arrhythmias in patients with prior history of cardiac injury[5-7]. However, their effects on LV mass, LVMI, and RWT are not well known. In this study, we investigated the effect of candesartan treatment in comparison with zofenopril, an inhibitor of the angiotensin-converting enzyme (ACE), on LV mass, LVMI, and RWT in post-MI patients.

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METHODS

Study design and population

In this prospective study, patients aged ≥18 years presenting with acute MI who underwent successful percutaneous coronary intervention (PCI) between January 2018 and January 2020 were recruited. Diagnosis of acute MI was defined based on criteria by the European Society of Cardiology[8]. Patients with prior history of coronary artery disease, end-stage renal disease, liver failure, coagulopathy, cardiogenic shock, and pregnancy were excluded from the study. Patients taking an ACE inhibitor or ARB at presentation or patients intolerant to ACE inhibitor or ARB treatment were also excluded. After successful PCI, patients were randomly assigned to a candesartan group or zofenopril group by using a sealed envelope system. The candesartan or zofenopril therapy started within 24 h following hospital admission. The initial doses of candesartan and zofenopril therapies were 4 and 7.5 mg, respectively. According to our study protocol, the initially given doses of candesartan and zofenopril were doubled every 2 weeks up to maximum doses of 32 and 60 mg, respectively. Whenever a sign of drug intolerance was observed, the dose was decreased to the previous level at which the subject was confirmed to be free of drug-related symptoms. After randomization, all subjects were evaluated before the start of treatment along with 1- and 6-month follow-ups. Patients' demographics, medical history, anthropometric measurements, medications, and electrocardiographic and echocardiographic measurements were recorded. Informed consent was obtained from all patients in accordance with the ethical guidelines of the 1975 Declaration of Helsinki protocol and approved by the Ethics Committee of Konya Selçuk University (approval number: 2019/138, date: May 22, 2019).

Coronary angiograms

PCI procedures were performed through the femoral or radial artery using 6 or 7 Fr sheaths. All patients were treated with dual antiplatelet therapy including aspirin (162–325 mg) and clopidogrel (300 mg for patients <75 years of age and 75 mg for patients >75 years of age) loading dose or ticagrelor (180 mg) loading dose prior to the procedure. Aspirin was continued indefinitely, and clopidogrel or ticagrelor was recommended for 12 months. Other medications, including beta-blockers, nitrates, and statins, were prescribed according to standardized protocols. Intravenous heparin was administered to achieve an activated clotting time of 300 s. Adjunctive pharmacotherapies, the type of stent, and the use of predilatation and postdilatation were at the discretion of the interventional cardiologist. Epicardial coronary blood flow was quantified visually using the Thrombolysis in Myocardial Infarction (TIMI) flow grade classification[9]. Procedural success was defined as residual stenosis <20% and TIMI flow grade 3.

Echocardiographic evaluation

During the echocardiographic examination, parasternal long-axis, short-axis, and apical four-chamber and two-chamber images were obtained and evaluated using M-mode, two-dimensional (2D), continuous-wave Doppler, pulse-wave Doppler, and tissue Doppler methods according to the American Echocardiography Society criteria[10]. M-mode and standard 2D echocardiographic evaluation were performed on all patients with transthoracic echocardiography using Vivid S5 (GE Healthcare, Horten, Norway) 1–3 MHz transducer. All measurements were performed by a cardiologist who was blind to the patient data and study protocol and verified by a second physician to avoid error in measurements. In our study, the Devereux equation, i.e., LV mass=0.8´[1.04´(interventricular septal thickness+LV end-diastolic diameter+posterior wall thickness)^3–(LV end-diastolic diameter)^3]+0.6 (g), was used to calculate LV mass[11]. LVMI was calculated by dividing an individual's LV mass by body surface area (body weight$^{0.425}$´height$^{0.725}$´0.007184)[12]. RWT was also calculated by using the following formula: 2´(posterior wall thickness/LV end-diastolic diameter).

Statistical analysis

Data were analyzed using the SPSS version 21.0 software for Windows (IBM SPSS Statistics for Windows, version 21.0.; IBM Corp., Armonk, NY, USA). In this study, data are expressed as mean±SD and median (interquartile ranges at the 25–75th percentiles, IQR) for continuous variables and as counts and percentages for categorical variables. The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to evaluate the distribution of continuous variables. The χ^2 test and Fisher's exact test were used to analyze categorical variables. Student's t-test was used for continuous variables with normal distribution and the values were presented as mean±SD. A comparison of intergroup continuous variables without normal distribution was analyzed using Mann-Whitney U test. In all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Initially, 246 patients were invited to participate in the study, of whom 217 gave their consent. Notably, 17 participants were excluded from the study due to treatment discontinuation. Therefore, 200 patients were finally included in the study. All patients were to be randomized in a 1:1 ratio to candesartan or zofenopril treatment. The baseline demographic and clinical characteristics of the study population are summarized in Table 1.

Table 1. Comparison of the baseline clinical characteristics and laboratory parameters of the groups.

Variable	Zofenopril (n=100)	Candesartan (n=100)	p-value
Age, years	56.74±10.58	59.08±12.38	0.153
Male gender, n %	84	77	0.212
Body mass index (kg/m^2)	27.83±3.35	28.60±4.32	0.162
Hypertension, n %	36	48	0.086
Smoking, n %	62	59	0.664
STEMI, n %	47	46	0.887
Systolic blood pressure (mmHg)	119.35±13.88	122.80±21.09	0.173
Diastolic blood pressure (mmHg)	73.25±9.62	74.80±13.16	0.343
Medicine			
Acetylsalicylic acid, n %	100	100	
ADP receptor antagonists, n %	100	100	
Beta-blocker (metoprolol), n %	100	100	
Metoprolol dose (mg)	55.0±21.61	57.75±18.69	0.337
Mineralocorticoid receptor antagonists, n %	7	8	0.788
Statins (atorvastatin/rosuvastatin)	29/71	86/14	0.000
Zofenopril dose (mg)	32.21±7.87		
Candesartan dose (mg)		14.28±5.53	
Blood parameters			
Hb, g/dL	15.06±1.59	14.49±1.93	0.023
WBC, $10^3/\mu L$	11.40±3.39	11.26±4.80	0.823
Platelet, $10^3/\mu L$	260.52±89.76	259.76±73.13	0.948
Glucose, (mg/dL)	144.47±70.42	158.09±79.82	0.202
e-GFR (mL/min/1.73 m^2)	91.42±23.13	89.52±22.00	0.552
Creatinine (mg/dL)	0.83 (0.74–1.03)	0.89 (0.73–1.02)	0.984
Total cholesterol (mg/dL)	194.60±50.32	194.01±50.53	0.934
HDL-C (mg/dL)	39.67±10.26	39.08±10.30	0.685
LDL-C (mg/dL)	120.43±43.11	123.28±42.50	0.638
Triglyceride (mg/dL)	145.00 (105.25–224.75)	148.0 (91.50–203.5)	0.475
Echo parameters			
LVEF (%)	50.12±8.87	48.16±8.51	0.113
LVIDd (mm)	51.57±4.89	50.68±3.99	0.161
LVIDs (mm)	34.44±6.64	34.09±5.59	0.688
PWD (mm)	10.40±1.09	10.64±1.26	0.153
IVS (mm)	10.77±1.30	11.33±1.49	0.005
LAD (cm)	3.85±0.40	3.90±0.47	0.443
LWM (g)	207.52±41.61	212.69±40.82	0.779
LWMI (g/m^2)	104.50 (95.0–116.75)	106.0 (96.0–123.00)	0.625
RWT (cm)	0.39±0.05	0.41±0.06	0.017

HDL-C: high-density lipoprotein cholesterol; Hb: hemoglobin; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; STEMI: ST-segment elevation myocardial infarction; WBC: white blood cells; e-GFR: estimated glomerular filtration rate; LVIDd: left ventricular internal diameter end diastole; LVIDs: left ventricular internal diameter end systole; PWD: posterior wall thickness at end diastole; IVS: interventricular septal thickness at end diastole; LAD: left atrium diameter; LWM: LV mass; LWMI: LV mass index; RWT: relative wall thickness.

The mean age of the study population was 57.91±11.55 years, and 80.5% were male. There were statistically no significant differences between the two groups in terms of age, sex, body mass index (BMI), and clinical features (p>0.05). The mean maintenance dose was 14.8 mg for candesartan and 32.2 mg for zofenopril. Although cardiac medications were comparable between the two groups, the use of lipid-lowering medications was significantly different. According to our data, the majority of patients in the candesartan group received rosuvastatin therapy, while the majority of patients in the zofenopril group received atorvastatin therapy. As a result of the sealed envelope system that used for patient randomization, this difference occurred (Table 1).

With respect to echocardiographic measurements, baseline LV systolic functions were similar in both groups (p>0.05). Similarly, estimated LV dimension, LV mass, and LVMI were comparable between the two groups (p>0.05) (Table 1). Follow-up echocardiographic measurements revealed significant improvements in the candesartan group in terms of changes in LV end-systolic diameter, interventricular septum thickness, posterior wall thickness, and left atrium diameter (p<0.05). Similar changes in the abovementioned echocardiographic parameters were also obtained in the zofenopril group (p<0.05). Regarding echocardiographic indices of cardiac remodeling, candesartan group showed a significant reduction of estimated LV mass and LVMI at 6-month follow-up visit compared to baseline values [199.53±38.51 g vs. 212.69±40.82 g; 99.05 g/m^2 (90.00–116.5) vs. 106.0 g/m^2 (96.0–123.00), p<0.05]. This trend was also observed in the zofenopril group during the 6-month follow-up period [201.22±40.07 g vs. 207.52±41.61 g; 101.0 g/m^2 (92.25–111.75.0) vs. 104.50 g/m^2 (95.0–116.75), p<0.05]. Follow-up outcomes of echocardiographic measurements in both groups are summarized in Tables 2 and 3. According to our study, both classes of drugs had favorable effects on post-MI cardiac remodeling. However, the absolute benefit was more prominent in the candesartan group as compared to the zofenopril group. In our study, observed reduction in LV mass and LVMI during the 6-month follow-up period was significantly higher in the candesartan group as compared to the zofenopril group (13.16±2.63 g vs. 6.30±2.87 g; 6.47±1.38 g/m^2 vs. 1.94±1.29 g/m^2, p<0.05). In addition, the percent reduction in LV mass and LVMI was found to be significantly higher in the candesartan group than in the zofenopril group (5.35±1.17% vs. 2.01±1.38%; 5.15±1.16% vs. 1.07±1.36%, p<0.05). However, these reductions were not accompanied by any significant reduction of RWT (p>0.05).

DISCUSSION

In the present study, we investigated the effects of candesartan treatment in comparison with zofenopril treatment in patients with acute MI by using echocardiographic indices of cardiac remodeling. Our results indicate that favorable effects on post-MI cardiac remodeling were more prominent in candesartan treatment as compared to zofenopril treatment.

Table 2. Effects of candesartan on echocardiography parameters after 1 and 6 months treatment.

	Baseline candesartan	1 month candesartan	6 months candesartan	p-value*	p-value**	p-value***
LVIDd (mm)	50.68±3.99	50.37±3.84	50.25±4.16	0.133	0.125	0.519
LVIDs (mm)	34.09±5.59	33.31±5.59	33.14±6.26	0.007	0.016	0.516
PWD (mm)	10.64±1.26	10.54±1.20	10.46±1.08	0.025	0.017	0.171
IVS (mm)	11.33±1.49	11.09±1.40	10.77±1.39	0.001	0.000	0.000
LVEF %	48.16±8.51	49.51±8.36	50.35±8.35	0.000	0.000	0.006
LAD (cm)	3.90±0.47	3.89±0.49	3.92±0.48	0.793	0.541	0.185
LWM (g)	212.69±40.82	205.52±42.76	199.53±38.51	0.001	0.000	0.008
LWMI (g/m^2)	106.0 (96.0–123.00)	100.5 (93.250–117.0)	99.05 (90.00–116.5)	0.000	0.000	0.030
RWT (cm)	0.41±0.06	0.41±0.06	0.41±0.05	0.568	0.374	0.882
Height (cm)	167.74±7.43	167.88±7.44	167.69±7.40	0.332	0.320	0.159
Weight (kg)	80.60±12.30	80.56±12.09	80.94±12.37	0.370	0.224	0.347
Body mass index (kg/m^2)	28.60±4.32	28.53±4.20	28.79±4.33	0.235	0.165	0.421
Metoprolol dose (mg)	57.75±18.69	67.50±26.94	77.75±33.12	0.000	0.000	0.064
Candesartan dose (mg)	14.41±5.52	15.50±5.66	18.16±7.65	0.006	0.000	0.000

*Baseline vs. 1 month. **Baseline vs. 6 months. ***1 month vs. 6 months. LVIDd: left ventricular internal diameter end diastole; LVIDs: left ventricular internal diameter end systole ; PWD: posterior wall thickness at end diastole; IVS: interventricular septal thickness at end diastole; LAD: left atrium diameter; LVEF: left ventricular ejection fraction; LWM: LV mass; LWMI: LV mass index; RWT: relative wall thickness.

Table 3. Effects of zofenopril on echocardiography parameters after 1 and 6 months treatment.

	Baseline zofenopril	1 month zofenopril	6 months zofenopril	p-value*	p-value**	p-value***
LVIDd (mm)	51.57±4.89	51.40±5.08	51.28±5.37	0.393	0.255	0.493
LVIDs (mm)	34.44±6.64	33.94±6.78	33.64±7.22	0.095	0.109	0.478
PWD (mm)	10.40±1.09	10.33±1.12	10.33±1.11	0.109	0.264	0.989
IVS (mm)	10.77±1.30	10.66±1.31	10.53±1.21	0.139	0.024	0.107
LAD(cm)	3.85±0.40	3.82 ±0.43	3.83±0.44	0.225	0.458	0.697
LVEF %	50.12±8.87	50.72±8.99	50.99±9.27	0.041	0.022	0.320
LWM (g)	207.52±41.61	206.12±48.67	201.22±40.07	0.706	0.031	0.148
LWMI (g/m^2)	104.50 (95.0–116.75)	100.00 (94.0–115.75)	101.0 (92.25–111.75.0)	0.030	0.007	0.177
RWT (cm)	0.39±0.05	0.39±0.058	0.39±0.06	0.933	0.699	0.661
Height (cm)	168.98±7.22	168.89±7.29	169.04±7.32	0.181	0.622	0.170
Weight (kg)	79.64±11.66	79.72±11.66	79.92±11.62	0.545	0.405	0.585
Body mass index (kg/m^2)	27.83±3.35	27.86±3.34	27.97±3.53	0.159	0.205	0.314
Metoprolol dose (mg)	55.00±21.61	67.25±27.22	74.25±30.86	0.000	0.000	0.001
Zofenopril dose (mg)	32.23±7.91	33.82±10.06	38.29±13.49	0.025	0.000	0.000

*Baseline vs. 1 month. **Baseline vs. 6 months. ***1 month vs. 6 months. LVIDd: left ventricular internal diameter end diastole; LVIDs: left ventricular internal diameter end systole; PWD: posterior wall thickness at end diastole; IVS: interventricular septal thickness at end diastole; LAD: left atrium diameter; LVEF: left ventricular ejection fraction; LWM: LV mass; LWMI: LV mass index; RWT: relative wall thickness.

It has been well established that cardiac remodeling is associated with pathophysiological changes in cardiac myocytes and may contribute to the development of adverse cardiac events[13]. Despite various known factors, MI is the most common etiologic factor associated with cardiac remodeling. Myocardial injury secondary to MI not only induces morphological changes in the infarcted area but also causes LV eccentric hypertrophy[14,15]. In response to cardiac injury following MI, cellular and molecular alterations occurring in the infarcted area yield ventricular dysfunction and malignant ventricular arrhythmias[16-18]. According to previous reports, up to 50% of patients who suffer from ventricular dysfunction will die within 5 years following MI. Besides, the mortality rate could be higher among those who were hospitalized for cardiac failure following MI. The underlying mechanism is cardiac remodeling associated with malignant ventricular arrhythmias and sudden cardiac death[19,20]. Therefore, a better understanding of the factors associated with cardiac remodeling and administrating medical therapies that reverse this pathological condition and improve ventricular functions in post-MI patients are mandatory.

Randomized trials have shown the detrimental effects of angiotensin II on ventricular functions and have proved that inhibition of angiotensin II via a non-ACE-dependent pathway may ameliorate cardiac remodeling[21,22]. Therefore, the use of ARB not only reverses cardiac remodeling but also prevents adverse cardiac events. These favorable effects were confirmed by the Valsartan in Acute Myocardial Infarction (VALIANT) trial, which investigated the effects of valsartan administration in comparison with captopril treatment in post-MI patients experiencing LV systolic dysfunction[23]. In another study, Suzuki et al. found candesartan treatment to be more efficacious than ACE inhibitors in terms of preventing cardiac remodeling in patients presenting with MI[2]. Outcomes of our study consistent with previous reports revealed that candesartan treatment was more efficacious than ACE inhibitor treatment in terms of improving echocardiographic indices of cardiac remodeling after MI. With regard to echocardiographic indices of cardiac remodeling, we preferred LV mass, LVMI, and RWT in order to assess the effects of candesartan treatment on cardiac remodeling. Among the well-known parameters for the assessment of cardiac remodeling, LV mass, LVMI, and RWT have been well-established echocardiographic parameters to characterize cardiac remodeling and have been extensively validated in clinical practice. In addition, these variables not only give the most precise results but are also confirmed by various cardiac imaging modalities[3]. Furthermore, these geometrical indices are strongly associated with adverse cardiac events in various clinical conditions[24].

According to our study, the absolute reduction in echocardiographic indices of cardiac remodeling including LV mass and LVMI was more prominent in patients receiving candesartan treatment as compared to patients receiving

zofenopril treatment following MI ($p<0.05$). To the best of our knowledge, this is the first study demonstrating the inhibitory effects of candesartan on LV mass and LVMI in patients presenting with MI. Although both classes of drugs showed a decrease in RWT, this reduction did not reach a statistical significance ($p>0.05$).

Limitations

A major limitation of this study is that participants were observed over a relatively short period of time. Randomized trials with long-term follow-up can provide more detailed information about the long-term effects of candesartan treatment in patients presenting with MI. Although it is the largest study to date investigating the association between candesartan treatment and changes in echocardiographic indices of cardiac remodeling, it is nonetheless a relatively small, single-center study. Finally, the determination of LV mass, LVMI, and RWT was limited by the availability and interpretability of conventional echocardiographic measurements. Assessment of those parameters by cardiac magnetic resonance imaging (MRI) or computed tomography (CT) will provide more accurate results.

CONCLUSION

The present study highlights that both zofenopril and candesartan treatments have favorable effects on LV geometry. However, the observed reduction in LV mass and LVMI during the 6-month follow-up period was significantly higher in the candesartan group than in the zofenopril group. Our results suggest that early candesartan treatment following MI may potentially be useful in terms of improving post-MI cardiac remodeling.

AUTHORS' CONTRIBUTIONS

HT: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **AT**: Conceptualization, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **KD**: Investigation, Resources, Supervision, Visualization. **BBA**: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. **NA**: Investigation, Resources, Supervision, Visualization. **MUY**: Investigation, Resources, Supervision, Visualization. **MSA**: Data curation, Validation. **CA**: Data curation, Software, Validation. **OCP**: Data curation, Software, Validation. **AMT**: Data curation, Software, Validation.

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