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Effect of Combination Therapy With Simvastatin and Carvedilol in Patients With Left Ventricular Dysfunction Complicated With Acute Myocardial Infarction Who Underwent Percutaneous Coronary Intervention

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Background This study assessed the effects of combination therapy with simvastatin and carvedilol on clinical outcome in patients with left ventricular (LV) dysfunction after acute myocardial infarction (AMI).
Methods and Results The study retrospectively analyzed the data from 672 patients with LV dysfunction [LV ejection fraction (LVEF) <40%] complicated with AMI who underwent percutaneous coronary intervention (PCI). The patients were divided into 4 treatment groups: combination group (n=160), simvastatin only group (n=216), carvedilol only group (n=242), neither treatment group (n=54). At 6 months after PCI, the LVEF had improved most significantly in the combination group. During 1-year follow-up, cardiac death occurred most frequently in the neither treatment group compared with the other 3 groups (combination: 4%, simvastatin alone: 7%, carvedilol alone: 8%, neither: 17%, p<0.001 between neither treatment and other 3 groups). The results on major adverse cardiovascular events (MACE) showed that the combination of simvastatin and carvedilol was associated with a relative risk reduction of 53% (p<0.001), treatment with simvastatin alone with a relative risk reduction of 44% (p=0.001), and carvedilol alone with a relative risk reduction of 40% (p=0.003) compared with neither treatment. The independent predictors of 1-year MACE were neither treatment, elevated high sensitivity C-reactive protein (≥0.5 mg/dl), and old age (>70 years).
Conclusion Combination therapy with simvastatin and carvedilol had a positive impact on the endpoints of cardiovascular death and MACE and seems to have an additive beneficial effect on these endpoints in patients with LV dysfunction complicated with AMI who underwent PCI. (*Circ J* 2006; **70:** 1269 – 1274)

Key Words: Adrenergic β-antagonists; Coronary artery disease; Heart failure; Statins

Although mortality from coronary artery disease (CAD) is declining, the incidence of associated heart failure (HF) is rising.[1] Despite the effectiveness of lipid-lowering therapy and β-blockers in improving cardiovascular outcomes, many studies have demonstrated low treatment rates in patients with ischemic HF.[2]

Therapy with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) lowers the mortality and morbidity of CAD and other atherosclerotic vascular disease, as evidenced by multiple large-scale clinical trials.[3–6] Statins show potential therapeutic benefits to patients with ischemic or non-ischemic HF, irrespective of lipid levels.[7] On the other hand, some authors report potential adverse effects of statins in HF,[8] and a relationship between low serum cholesterol level and worse clinical outcomes in HF.[9]

Carvedilol is known not only as a vasodilating β-and α-blocker, but also as an antioxidant, and it may reduce the oxidative stress level in the human failing myocardium.[10] Previous studies have demonstrated that carvedilol prolonged survival and ameliorated the morbidity of patients with severe HF.[11–13]

However, little data are available about the effect of combining statin and β-blocker therapies on clinical outcome in patients with left ventricular (LV) dysfunction complicated with acute myocardial infarction (AMI) who undergo percutanous coronary intervention (PCI). We hypothesized that this combination would be associated with lower all-cause mortality and morbidity in such patients.

Methods

Study Population

This was a single-center, retrospective, non-randomized study. We studied 672 patients with LV dysfunction [LV ejection fraction (LVEF) <40%] complicated with AMI who underwent PCI between January 2000 and June 2004. Patients who underwent PCI for the treatment of AMI were included regardless of the type of PCI procedure such as primary, rescue, or elective. The patients were divided into 4 treatment groups: combination group (n=160, 61±11

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Table 1 Baseline Clinical Characteristics

	Simvastatin use (+) Carvedilol use (+) (n=160)	Simvastatin use (+) Carvedilol use (–) (n=216)	Simvastatin use (–) Carvedilol use (+) (n=242)	Simvastatin use (–) Carvedilol use (–) (n=54)
Age (years)	61±11	62±10	63±10	65±12*
Men	112 (70%)	156 (72%)	165 (68%)	40 (74%)
Hypertension	25 (40%)	76 (35%)	92 (38%)	20 (37%)
Diabetes mellitus	51 (32%)	65 (30%)	68 (28%)	14 (26%)
Smoker	77 (48%)	112 (52%)	128 (53%)	26 (49%)
Hyperlipidemia	94 (59%)†	134 (62%)†	97 (40%)	18 (33%)
Prior myocardial infarction	5 (3%)	4 (2%)	6 (2%)	1 (2%)
Prior percutaneous coronary intervention	7 (4%)	7 (3%)	9 (4%)	2 (4%)
Pain to door time (min)	209±168	219±176	226±178	209±166
Pain to balloon time (min)	422±398	429±331	431±338	419±306
Ejection fraction (%)	32±8	30±9	34±5	29±9
Multivessel disease	110 (69%)	152 (70%)	162 (67%)	38 (70%)
Atrial fibrillation	16 (10%)	17 (8%)	17 (7%)	6 (11%)
Simvastatin dose (mg)				
20	99 (62%)	138 (64%)		
40	61 (38%)	78 (36%)		
Carvedilol dose (mg)				
6.25	96 (60%)		150 (62%)	
12.5	56 (35%)		82 (34%)	
25	8 (5%)		10 (4%)	

*p<0.05 compared with simvastatin-treated group. †p<0.05 compared with non-simvastatin-treated group.

years, men 70%), simvastatin only group (n=216, 62±10 years, men 72%), carvedilol only group (n=242, 63±10 years, men 68%), neither treatment group (n=54, 65±12 years, men 74%). Patients with supine systolic arterial pressure <90 mmHg at admission, hemodynamically significant stenotic valvular heart disease, and hemodynamically significant dysrhythmia were excluded. Bedside echocardiography was performed for all patients before PCI or shortly after PCI and the LVEF was measured using the modified Simpson's method.

Medications

In the simvastatin group, the daily dose was 20 or 40 mg and was usually started immediately after PCI. In the carvedilol group, the daily dose was 6.25, 12.5 or 25 mg and was also usually started immediately after PCI. After PCI, all patients received aspirin (100 mg/day, indefinitely) and ticlopidine (250 mg/day continued for at least 6 months) or clopidogrel (75 mg/day continued for at least 6 months). Medications were assessed at baseline and every 4 weeks during clinic examinations. Medications, exact dates of initiation and cessation, and doses were recorded.

Laboratory Analysis

In all patients, serum was collected before PCI for measuring lipid profiles and high-sensitivity C-reactive protein (hs-CRP) levels, fibrinogen, and white blood cells and each fraction. All laboratory values were measured after an overnight fast. The serum levels of total cholesterol, triglyceride, low-density lopoprotein (LDL)-cholesterol, and high-density lopoprotein-cholesterol were measured by standard enzymatic methods. hs-CRP was assessed by the immunoturbidimetric CRP-Latex (II) hs assay using a Olympus 5431 autoanalyzer (Olympus, Tokyo, Japan). The assay was performed according to the manufacturer's protocol and has been validated against the Dade-Behring method.[14] Plasma fibrinogen level was quantified by means of the Clauss clotting assay (normal range: 150–450 mg/dl). Total white blood cells and each fraction were measured with a Coulter Gen S (Beckman Coulter, Miami, FL, USA) automated hematology analyzer. Laboratory analysis was performed at admission and repeated at 6 months after PCI.

PCI

Coronary angiography was performed via the femoral arteries. All implanted stents were bare metal and implantation was performed in the case of suboptimal results for percutaneous balloon angioplasty, residual stenosis >30%, intimal dissection, or as a bail-out procedure.[15,16] Dalteparin was administered at 120 units/kg body weight intravenously every 12 h or unfractionated heparin as an intravenous bolus (usually 5,000 units) followed by a continuous infusion at a dose adjusted according to the activated partial thromboplastin time.

Clinical Follow-up

After discharge, the patients were observed during 1-year follow-up for major adverse cardiovascular events (MACE), such as cardiac death, cerebrovascular accident, AMI, oir target lesion revascularization. Echocardiography was performed at admission and repeated at 6 months after PCI.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows, version 11.0 (Chicago, IL, USA) was used for all analyses. Results are presented as the mean value ± SD for continuous variables and as the percentage of total patients for categorical variables. Differences in baseline characteristics were evaluated using t-tests and chi-square statistics. Survival curves were calculated by the Kaplan-Meier method. Logistic regression analysis was used to identify the independent predictors of MACE. We defined elevated CRP level as hs-CRP ≥0.5mg/dl[17–19] and old age as >70 years.[20] A p-value <0.05 was considered as significant.

Table 2 Laboratory Findings

	Simvastatin use			
	(+) Carvedilol use		(–) Carvedilol use	
	(+) (n=160)	(–) (n=216)	(+) (n=242)	(–) (n=54)
Baseline				
Total cholesterol (mg/dl)	201±40	199±30	189±43	190±32
Triglyceride (mg/dl)	154±42	150±36	144±41	140±32
LDL-cholesterol (mg/dl)	144±34	146±28	135±31	133±28
HDL-cholesterol (mg/dl)	42±9	43±8	44±10	45±9
High sensitivigy C-reactive protein (mg/dl)	3.5±2.5	3.4±2.4	3.3±2.8	3.0±2.5
Fibrinogen (mg/dl)	293±74	281±89	287±65	281±80
White blood cell (mg/dl)	9,840±2,610	9,870±3,040	9,790±2,620	9,780±3,010
Monocyte (mg/dl)	878±335	870±280	868±321	860±270
6-month follow-up				
Total cholesterol (mg/dl)	159±38*	164±38*	178±33	194±30
Triglyceride (mg/dl)	120±40*	124±30*	154±40	150±30
LDL-cholesterol (mg/dl)	98±34*	100±32*	123±34	128±38
HDL-cholesterol (mg/dl)	52±9*	49±10*	45±9	43±8
High sensitivigy C-reactive protein (mg/dl)	0.6±2.5*	0.7±2.4*	0.9±1.5	1.4±1.4
Fibrinogen (mg/dl)	255±74*	259±89*	275±74	285±89
White blood cell (mg/dl)	7,050±1,390*	7,200±3,020	7,340±2,650	7,400±3,040
Monocyte (mg/dl)	452±220*	456±218*	523±180	580±178

*p<0.05 compared with neither treatment.
LDL, low-density lopoprotein; HDL, high-density lopoprotein.

Results

Baseline Clinical Characteristics (Table 1)

The mean age was highest in the neither treatment group and hyperlipidemia was more frequently observed in the simvastatin group than in the other treatment groups. The daily dose of simvastatin was 20 mg in 62% and 64%, and 40 mg in 38% and 36% in the combination group and simvastatin only group, respectively. The daily dose of carvedilol was 6.25 mg in 60% and 62%, 12.5 mg in 35% and 34%, and 25 mg in 5% and 4% in the combination group and carvedilol only group, respectively. Other medications were not different among the 4 groups.

Laboratory Findings

Baseline and 6-month follow-up laboratory data are shown in Table 2. At 6 months after PCI, simvastatin treatment significantly decreased the LDL-cholesterol, hs-CRP and fibrinogen levels, and the monocyte count. The combination therapy showed the most significant improvement in lipid profiles and inflammatory markers.

LV Systolic Function

At 6 months after PCI, LVEF was most significantly improved in the combination group. From baseline to 6-month follow-up, LVEF improved from 32±8% to 42±8% in the combination group, 30±9% to 38±7% in the simvastatin only group, 34±5% to 40±7% in the carvedilol only group, and 29±9% to the 32±6% in neither treatment group. Compared with baseline LVEF, it improved by 31%, 27%, 24%, and 10%, respectively, in the combination group, simvastatin only group, carvedilol only group, and neither treatment group at 6-month follow-up (Fig 1).

MACE (Table 3)

During the 1-year follow-up, 50 patients died, 11 patients had a cerebrovascular accident, 29 patients had a re-infarction and target lesion revascularization was performed in 136 patients. Combination therapy was associated with a 77% relative risk reduction (p<0.001), simvastatin alone with a 59% relative risk reduction (p<0.001), and carvedilol alone with a 50% relative risk reduction (p<0.001) of cardiac death compared with neither treatment. Combination therapy was associated with a 53% relative risk reduction (p<0.001), simvastatin alone with a 44% relative risk reduction (p=0.001), and carvedilol alone with a 40% relative risk reduction (p=0.003) of 1-year MACE compared with neither treatment (Fig 2).

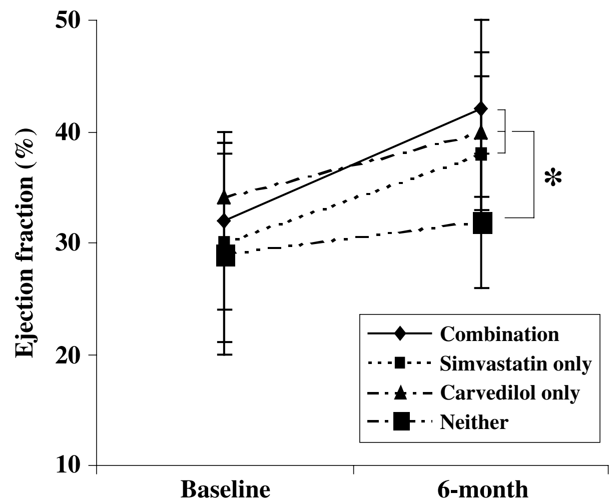

Fig 1. Changes in the left ventricular ejection fraction at 6 months after percutaneous coronary intervention. *p<0.05 compared with neither treatment.

Independent Predictive Factors of MACE (Table 4)

Variables tested included: age; diabetes mellitus; LVEF; angiographic minimal lumen diameter; hs-CRP level; monocyte count; treatment with simvastatin and carvedilol. In the multivariate analysis, the independent predictors of 1-year MACE were neither treatment, elevated hs-CRP

Table 3 Major Adverse Cardiovascular Events at 1-Year After Percutaneous Coronary Intervention

	Simvastatin use (+)		*Simvastatin use (–)*	
	Carvedilol use		*Carvedilol use*	
	(+) (n=160)	*(–) (n=216)*	*(+) (n=242)*	*(–) (n=54)*
Cardiac death	*6 (4%)**	*15 (7%)**	*20 (8%)**	*9 (17%)*
Cerebrovascular accident	*2 (1%)*	*3 (1%)*	*4 (2%)*	*2 (4%)*
Repeat myocardial infarction	*4 (3%)*	*10 (5%)*	*11 (5%)*	*4 (7%)*
Target lesion revascularization	*30 (19%)*	*43 (20%)*	*50 (21%)*	*13 (24%)*
Event-free survival (%)	*125 (78%)**	*160 (74%)**	*175 (72%)**	*29 (54%)*

**p<0.05 compared with neither treatment.*

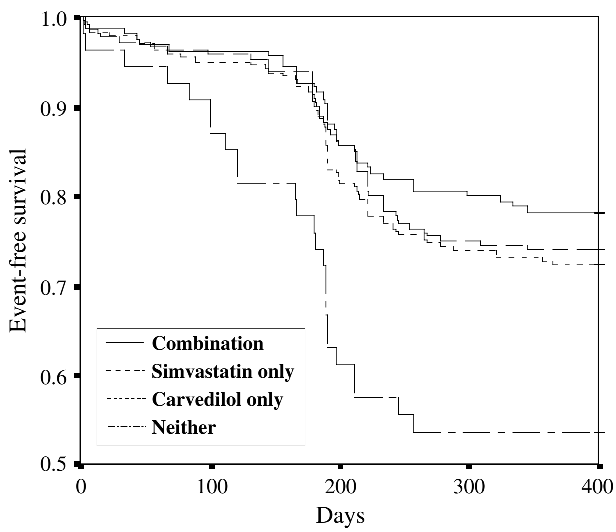

Fig 2. Kaplan-Meier survival curve.

(≥0.5 mg/dl), and old age (>70 years).

Discussion

We have demonstrated that combination therapy with simvastatin and carvedilol decreased morbidity and mortality in patients with LV dysfunction complicating AMI who underwent PCI. Our results suggest that the combination has an additive beneficial effect on improving LV function and reducing morbidity and mortality.

We previously reported that simvastatin therapy lowered cardiac mortality in patients with ischemic HF complicating AMI who underwent PCI.[19] Horwich et al[7] studied the impact of statin therapy in a cohort of 551 patients with systolic HF (LVEF ≤40%). They showed that statin therapy was associated with improved survival without the necessity for urgent heart transplantation in both ischemic and non-ischemic HF patients and that statin therapy was an independent predictor of improved survival. Mozaffarian et al[21] evaluated the effects of statin therapy in 1,153 patients with severe HF (LVEF <30% and New York Heart Association (NYHA) class IIIB or IV symptoms) of ischemic and non-ischemic etiologies. They showed that statin therapy was associated with a 62% lower risk of death or 1 fewer death/5 patients taking statin therapy for 1 year after adjusting for age, gender, diabetes, smoking, HF etiology, LVEF, and NYHA class.

Statins inhibit mevalonate synthesis and effectively lowers LDL-cholesterol. Beyond lowering lipids, statins have favorable effects on vascular inflammation,[22,23] endothelial function,[24,25] and platelet adhesion and thrombosis.[26] The anti-atherothrombotic effects of statins clearly have potential benefit for patients with CAD-associated HF. Statins promote atherosclerotic plaque stabilization via inhibition of inflammatory macrophages, depletion of the lipid core, and strengthening of the fibrous cap. The mechanism for atherosclerotic plaque rupture and the impact of statins on plaque stabilization could reasonably be expected to be similar between patients with and without HF. Statins are now recognized as anti-inflammatory agents that downregulate inflammatory cytokines and CRP.[27–29] Experimental studies in models of myocardial ischemia/reperfusion injury have demonstrated that statin treatment reduces the extent of myocardial necrosis, preserves myocardial viability, and results in improved ventricular function.[30]

Carvedilol is known not only as a β- and α-adrenergic-blocking drug but also as an antioxidant. The American Heart Association and American College of Cardiology (AHA/ACC) guidelines for secondary prevention of myocardial infarction (MI) recommend initiating β-adrenoceptor blockade in all post-MI patients and continuing the

Table 4 Multivariate Predictive Factors of Major Adverse Cardiovascular Events

	Odds ratio	*95%CI*	*p value*
Neither treatment	*10.1*	*3.4–20.6*	*<0.001*
High sensitivity C-reactive protein ≥0.5 mg/dl	*6.2*	*2.9–12.3*	*0.008*
Old age (>70 years)	*4.4*	*2.4–9.2*	*0.014*
Diabetes mellitus	*1.4*	*0.8–1.8*	*0.109*
LVEF	*0.8*	*0.6–1.4*	*0.142*
MLD	*0.9*	*0.7–1.2*	*0.328*
Monocyte count	*1.1*	*0.8–1.3*	*0.394*

CI, confidence interval; LVEF, left ventricular ejection fraction; MLD, minimal lumen diameter.

therapy indefinitely.[31] Beta-adrenoceptor antagonist therapy results in reduction of myocardial oxygen demand and is therefore also effective for the treatment of CAD. Carvedilol inhibits lipid peroxidation and prevents cardiac contractile dysfunction,[32] and it inhibits mitochondrial oxygen consumption and superoxide production during calcium overload in isolated heart mitochondria,[33] and it may reduce the oxidative stress level in the human failing myocardium.[10] Packer et al[12] reported that in euvolemic patients with symptoms of HF at rest or on minimal exertion, the addition of carvedilol to conventional therapy ameliorated the severity of HF and reduced the risk of clinical deterioration, hospitalization, and other serious adverse clinical events. Because chronic β-adrenergic receptor signaling is the dominant cardiotoxic pathway in the failing heart, effective β-adrenergic receptor blockade by carvedilol is thought to be especially important.[34] Carvedilol also has an antiarrhythmic property. Experimentally, carvedilol reduces complex and repetitive ventricular ectopy induced by ischemia and reperfusion. In patients with atrial fibrillation and HF, carvedilol reduced mortality risk and improves LV function.[35] In the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study,[36] carvedilol showed a powerful antiarrhythmic effect after AMI, even in patients already treated with an angiotensin-converting enzyme inhibitor. Carvedilol suppressed atrial as well as ventricular arrhythmias in these patients. Carvedilol also has salutary effects on progressive LV remodeling and functional deterioration.[34,37]

Despite the effectiveness of statin and carvedilol in altering subsequent cardiovascular mortality, studies have documented low treatment rates in patients with established CAD.[2] Hognestad et al[38] reported that early initiation of statin or β-blocker therapy was associated with improved event-free survival, and that the benefits of the combined treatment were additive. They demonstrated that the combination of statins and β-blockers was associated with a 48.3% relative risk reduction compared with neither treatment.

Study Limitations

A major limitation of this study is that it was not preplanned and was retrospective, so the patients were not randomized to receive simvastatin or carvedilol. Obviously, there was some selection bias among patients receiving simvastatin and carvedilol, which is evident from the difference in some of the baseline demograpthe 4 groups and hyperlipidemia was more frequently observed in the simvastatin-treated group than that in the no-simvastatin-treated group. These findings support the need for prospective, randomized, blinded, placebo-controlled trials to determine whether the combination therapy will benefit patients with ischemic HF.

Conclusions

Our study results show that combination therapy with simvastatin and carvedilol was associated with a 77% relative risk reduction of cardiac death and with a 53% relative risk reduction of MACE compared with neither treatment. This suggests an additive beneficial effect of the combination therapy in patients with LV dysfunction complicating AMI who undergo PCI.

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