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The Long-Term Clinical Outcomes of Combination Therapy with Angiotensin II Type 1 Receptor Blocker and Simvastatin after Percutaneous Coronary Intervention

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ABSTRACT

Background and Objectives : Angiotensin II type 1 receptor blocker (ARB) has been to attenuate neointimal formation and vascular smooth muscle cell proliferation, with decreased inflammation. Recent studies have demonstrated that statins may contribute to the beneficial effects of ARB toward vascular diseases. The aim of this study was to evaluate the beneficial effects of the combination therapy of ARB and statin compared to that of angiotensin converting enzyme (ACE) inhibitor and statin in acute coronary syndrome (ACS) patients who underwent percutaneous coronary intervention (PCI). **Subjects and Methods :** 396 patients with ACS, who underwent PCI between June 2002 and December 2003, were divided into two groups: the ARB and simvastatin (n=188, 61.2±10.3 years, male 72%) and ACE inhibitor and simvastatin groups (n=208, 60.9±10.6 years, male 66%). The major adverse cardiovascular events, including restenosis and repeat PCI, between the two groups were compared. **Results :** At 6-month after PCI, the levels of total cholesterol, triglyceride and low-density lipoprotein cholesterol were significantly decreased and that of high-density lipoprotein cholesterol significantly increased, and the levels of high-sensitivity C-reactive protein, fibrinogen, white blood cell and monocyte significantly decreased in both groups. A quantitative coronary angiography analysis of stented coronary segments disclosed no differences in the minimum lumen diameter and stent length. At the 6-month follow-up angiogram, there were no significant differences in the incidence of restenosis and repeat PCI, and there was also no difference in late loss between the two groups (ARB and statin group: 20%, 18%, 0.78±0.38 mm vs. ACE inhibitor and statin group: 22%, 20%, 0.81±0.44 mm). There were no significant differences in the incidence of cardiac deaths, myocardial infarctions, cerebrovascular accidents and bypass grafts at the 1-year clinical follow-up between the two groups. The event-free survival rates at 1 year were 81 and 79% in the ARB and statin and the ACE inhibitor and statin groups, respectively. There were no differences in the late loss and major adverse cardiac events according to the used ARBs or ACE inhibitors. **Conclusion :** The combination therapy of ARB with statin might not show more beneficial effects compared to ACE inhibitor with statin in ACS patients having undergone PCI. **(Korean Circulation J 2005;35:877-882)**

KEY WORDS : Angiotensin converting enzyme inhibitor ; Statins.

Introduction

Angiotensin II induces many vascular effects, including vasoconstriction, inflammation, vascular remodeling, thrombosis and plaque rupture.[1)2)] The rennin-angiotensin system (RAS) makes important contributions to

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a variety of cardiovascular diseases, and is the target of angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB). The selective and potent inhibition of angiotensin II by ARBs can prevent end-organ damage due to hypertension-associated diseases, such as coronary heart disease, atherosclerosis and renal disease, with these effects appearing to be potentially independent of their blood pressure lowering effects.[3-5]

Recent large clinical trials have demonstrated that the therapeutic use of statins resulted in decreased incidences of ischemic stroke and myocardial infarction, and a reduction in the mortality of hypercholesterolemic subjects.[6][7] The effects of statins have mainly been attributed to their cholesterol-lowering properties, but there is growing evidence that some of the beneficial effects of these agents may be independent of the plasma cholesterol level.[8]

There is a strong rationale for combining an ARB with a statin. Recent studies have demonstrated that statins may prevent angiotensin II-induced cellular and organ damage, such as the production of reactive oxygen species in vascular smooth muscle cells, cardiac hypertrophy and end-organ damage.[9][10] ACE inhibitors also improve vascular reactivity and reduce structural damage in hypercholesterolemic hypertensive subjects, with the beneficial effect of ACE inhibitors being evident in patients undergoing concomitant statin therapy.[11]

However, no trials testing a combination of ARBs with statins have been conducted. Therefore, the beneficial effects of the combination therapy of ARBs and statin were evaluated and compared to the combination therapy of ACE inhibitors and statin in acute coronary syndrome (ACS) patients having undergone percutaneous coronary intervention (PCI).

Subjects and Methods

Study design and population

Our patient population consisted of 396 patients with unstable angina and non-ST segment elevation myocardial infarction, who had undergone PCI between June 2002 and December 2003. The patients were divided into two groups; the ARB and simvastatin (61.2±10.3 years, male 72%), ACE inhibitor and simvastatin groups (60.9±10.6 years, male 66%). The ARBs used were irbesartan (35%), losartan (32%), valsartan (20%) and telmisartan (13%), and the ACE inhibitors used were ramipril (40%), enalapril (32%) and captopril (28%). The dosage of simvastatin was 20 mg in 60 and 63% of the patients in the ARB and simvastatin and ACE inhibitor and simvasatatin groups, and 40 mg in 40 and 37% of the patients in the ARB and simvastatin and ACE inhibitor and simvasatatin groups, respectively.

Laboratory analysis

Serum was collected from all patients immediately before the initial PCI to measure the lipid profiles, high-sensitivity C-reactive protein (hs-CRP) levels and monocyte count. Blood sampling was carefully and gently performed to avoid hemolysis. hs-CRP was assessed by the immunoturbidimetric CRP-Latex (II) hs assay, using an Olympus 5431 autoanalyzer (Denka Seiken, Japan). The assay was performed according to the manufacturer's protocol, and was validated against the Dade-Behring method.[12] The total white blood cells in each fraction were measured using a Coulter Gen S automated hematology analyzer (Beckman Coulter, USA). The lipid profiles and inflammatory markers, such as hs-CRP, fibrinogen, and white blood cell and monocyte counts were measured at 6-months after PCI, and compared with the initial baseline levels.

Stent implantation procedure

Stent implantation was performed as previously described.[13] All implanted stents were of the bare metallic kind. All patients received aspirin (300 mg at least 12 h prior to stent implantation and 100-200 mg daily, indefinitely) and ticlopidine (500 mg at least 6 h prior to stent implantation and 250 mg daily, which was continued for 30 days) or clopidogrel (300 mg at least 6 h prior to stent implantation and 75 mg daily, which was continued for 30 days). A coronary angiogram was performed through the femoral or radial artery. Dalteparin was intravenously administered at 120 U per kilogram of body weight every 12 hours, or unfractionated heparin as an intravenous bolus (usually 5000 units), followed by a continuous infusion at a dose adjusted according to the activated partial thromboplastin time. All stenotic lesions were pre-dilated and the stents deployed at 10 to 18 atm.

Quantitative Coronary Angiography (QCA)

The angiograms were analyzed using a validated QCA system (Phillips H5000 or Allura DCI program). The minimal lumen, reference and percent diameters of stenosis were measured in identical views before the percutaneous balloon angioplasty and immediately after the stent implantation.

Ascertainment of major adverse cardiovascular events

The patients were observed for major adverse cardiac events (MACE), such as cardiac death, acute myocardial infarction, cerebrovascular accident, repeat PCI and bypass graft, during the follow-up period. Angiographic restenosis was observed at 6 months after PCI and MACE during the 1 year clinical follow-up. Angio-

graphic restenosis was defined as stenosis of more than 50% of the target lesion on the follow-up coronary angiogram.

Statistical analysis

The results are presented as the mean value±SD for the continuous variables, and as the percentage of total patients for the categorical variables. Differences in baseline characteristics were evaluated using *t*- and chi-squared statistical tests. The statistical Package for Social Sciences (SPSS) for Windows, version 11.0 (Chicago, Illinois) was used for all analyses.

Results

Baseline characteristics

The baseline clinical characteristics are summarized in Table 1. There were no significant differences in the demographic data and medications after PCI.

Table 1. Baseline clinical characteristics

	ARB+statin (n=188)	ACE inhibitor +statin (n=208)	p
Age (yours)	61.2±10.3	60.9±10.6	0.397
Men (%)	136 (72)	138 (66)	0.197
Hypertension (%)	77 (41)	92 (44)	0.647
Diabetes mellitus (%)	60 (32)	58 (28)	0.541
Smoker (%)	98 (52)	119 (57)	0.441
Hyperlipidemia (%)	111 (59)	110 (53)	0.443
Clinical diagnosis (%)			0.623
Unstable angina	139 (74)	162 (78)	
Non-ST elevation myocardial infarction	49 (26)	46 (22)	
Left ventricular ejection fraction (%)	62.2±10.9	63.0±8.4	0.321
Prior PCI (%)	17 (9)	19 (9)	0.826
Other medication after PCI (%)			
Aspirin	184 (98)	202 (97)	0.572
ADP-receptor blocker	132 (70)	150 (72)	0.747
Beta-blocker	143 (76)	156 (75)	0.938
Diuretics	71 (38)	81 (39)	0.798
Nitrate	62 (33)	60 (29)	0.892
ARB (%)			
Irbesartan	66 (35)		
Losartan	60 (32)		
Valsartan	38 (20)		
Telmisartan	24 (13)		
ACEI (%)			
Ramipril		83 (40)	
Enalapril		67 (32)	
Captopril		58 (28)	
Dosage of simvastatin (%)			
20 mg	113 (60)	130 (63)	0.543
40 mg	75 (40)	78 (37)	0.528

ARB: angiotensin receptor blocker, ACE: angiotensin converting enzyme, PCI: percutaneous coronary intervention, ADP: adenosine diphosphate

Angiographic and QCA results

The angiographic results are summarized in Table 2. There were no significant differences in the diagnostic coronary angiographic findings. The QCA and procedural results are summarized in Table 3. There were no significant differences in the minimal lumen diameters, lesion lengths and acute gains. On the 6-month follow-

Table 2. Coronary angiographic findings

	ARB+statin (n=188)	ACE inhibitor +statin (n=208)	p
Target coronary artery (%)			0.458
Left anterior descending artery	143 (76)	137 (66)	
Left circumflex artery	19 (10)	33 (16)	
Right coronary artery	26 (14)	38 (18)	
Diseased vessel number (%)			0.270
1	90 (48)	133 (64)	
2	56 (30)	42 (20)	
3	42 (22)	33 (16)	
ACC/AHA type			0.282
B1	83 (44)	79 (38)	
B2	38 (20)	71 (34)	
C	77 (36)	58 (28)	
TIMI flow (%)			0.712
0	19 (10)	17 (8)	
I	11 (6)	17 (8)	
II	38 (20)	33 (16)	
III	120 (64)	141 (68)	

ARB: angiotensin receptor blocker, ACE: angiotensin converting enzyme, ACC/AHA: American College of Cardiology/American Heart Association, TIMI: thrombolysis in myocardial infarction

Table 3. Quantitative coronary angiographic and procedural results

	ARB+statin (n=188)	ACE inhibitor +statin (n=208)	p
Reference vessel diameter (mm)	3.17±0.70	3.19±0.50	0.898
Minimal luminal diameter (mm)	0.55±0.30	0.58±0.30	0.556
Diameter stenosis (%)	82.6±8.2	81.8±10.2	0.691
Lesion length (mm)	19±5	18±7	0.978
Stent length (mm)	23±10	22±12	0.983
Number of used stent	2.5±1.6	2.4±1.8	0.278
Post-stenting minimal lumen diameter (mm)	3.28±0.80	3.24±0.50	0.349
Acute gain (mm)	2.73±0.62	2.66±0.57	0.424
6-month follow-up minimal luminal diameter (mm)	2.01±0.57	1.95±0.48	0.478
6-month follow-up diameter stenosis (%)	32.1±22.1	34.2±20.3	0.683
Late loss (mm)	0.78±0.38	0.81±0.44	0.465

ARB: angiotensin receptor blocker, ACE: angiotensin converting enzyme

up angiograms, the average late losses were 0.78±0.38 and 0.81±0.44 mm in the ARB and simvastatin and ACE inhibitor and simvastatin groups, respectively.

The change of lipid profiles and inflammatory markers

At 6-months after PCI, the levels of total cholesterol, triglyceride and low-density lipoprotein cholesterol were significantly decreased in both groups, and that of the high-density lipoprotein cholesterol was significantly increased in both groups (Fig. 1). Also, at 6-months after PCI, the levels of hs-CRP, fibrinogen, white blood cells and monocytes were significantly decreased in both groups (Fig. 2). There were no significant differences in the follow-up lipid profiles and inflammatory markers between the two groups.

The incidence of restenosis and repeat PCI

When a categorical criterion of ≥50% diameter stenosis at follow-up was used to assess restenosis development, the restenosis rates were 20 and 22% in the ARB and simvastatin and ACE inhibitor and simvastatin groups, respectively. The revascularization rates were 18 and 20% in the ARB and simvastatin and ACE inhibitor and simvastatin groups, respectively, but these were not statistically significant (Fig. 3). The restenosis rate ranged between 18 and 23%, and that of the repeat PCI rate was between 16 and 21%, in relation to the ARBs or ACE inhibitors used. There were no differences in the restenosis and repeat PCI rates according to the use of the individual agents.

The incidence of major adverse cardiovascular events

During the 1-year clinical follow-up period, there were no significant differences in the incidences of cardiac deaths, myocardial infarctions, cerebrovascular accidents and bypass grafts. The MACE-free survivals were 81 and 79% in the ARB and simvastatin and ACE inhibitor and simvastatin groups, respectively (Fig. 4). The incidence of MACE ranged between 17 and 22%, in relation to the ARBs or ACE inhibitors used. There was no difference in MACE-free survival according to the use of the individual agents.

Discussion

Despite a strong rational for combining an ARB with a statin, very few in vivo studies have addressed the beneficial effects of these types of combination therapy. Also, little data are available on the comparative study between the combinations of either an ARB or an ACE inhibitor with statins. Better results were expected with the ARB and statin than the ACE inhibitor and statin combination; however, no greater beneficial effects were shown with the combination therapy of ARB and simvastatin compared to ACE inhibitor with simvastatin in ACS patients having undergone PCI.

Atherosclerosis is characterized by chronic inflammation of the vascular wall. Inflammation plays an important role in the destabilization of the atherosclerotic plaque and the development of vascular events. There is good evidence from epidemiological, laboratory and clinical studies for the contribution of RAS to atherosclerosis, not only from the increase of blood pressure, but also through multiple direct effects on the arterial walls. Activation of oxidative stress by angiotensin II is a key component of this process.[14]

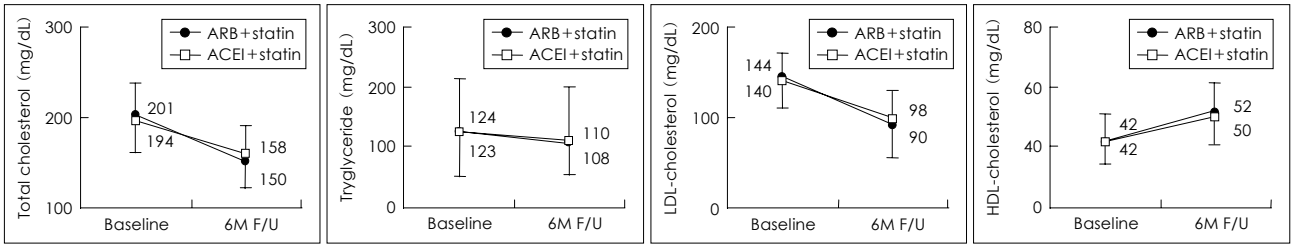

Fig. 1. The change in the lipid profiles at 6-month after percutaneous coronary intervention. At the 6 month follow-up, all lipid profiles were significantly improved in both groups ($p<0.001$ in above four lipid parameters in both groups). ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

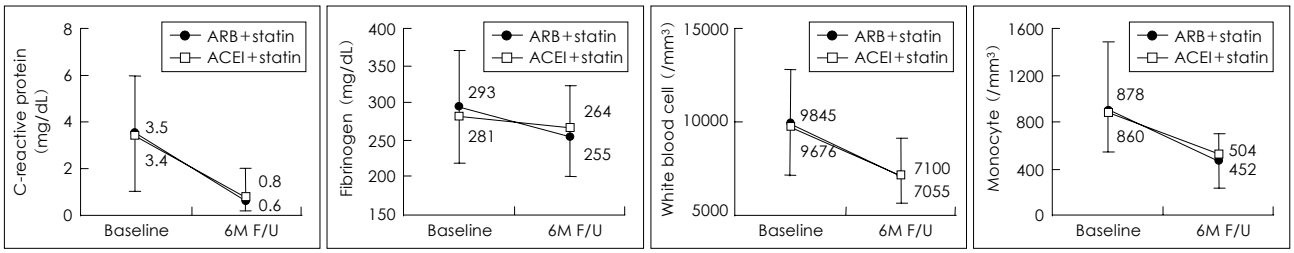

Fig. 2. The change in the inflammatory markers at 6-months after percutaneous coronary intervention. At the 6 month follow-up, all inflammatory markers were significantly improved in both groups ($p<0.001$ in the above four inflammatory markers in both groups). ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor.

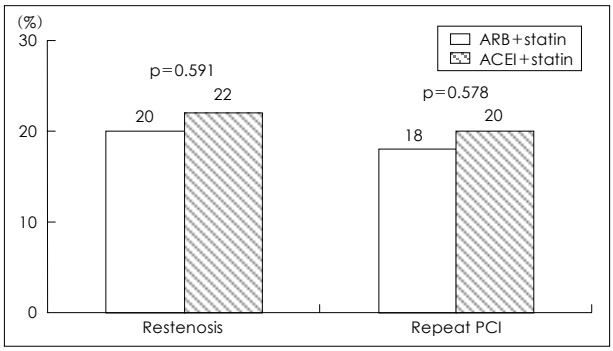

Fig. 3. The restenosis and repeat percutaneous coronary intervention (PCI) rates. ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor.

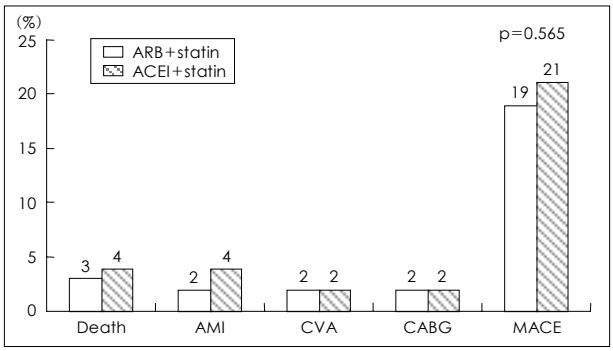

Fig. 4. The major adverse cardiac events (MACE). ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor, AMI: acute myocardial infarction, CVA: cerebrovascular accident, CABG: coronary artery bypass graft.

The administration of an ARB has been observed to reduce the generation of reactive oxygen species in animal models, which inhibited fatty streak formation through the inhibition of proliferative and inflammatory response mechanisms in diet-induced hypercholesterolemia.[15] ARBs have beneficial effects in patients with coronary artery disease and atherosclerosis, even in those with ischemic heart failure.[16] Six months treatment with valsartan significantly reduced the rate of restenosis following coronary stenting.[17] The administration of losartan significantly improved the flow-mediated coronary dilation during stress in patients with atherosclerosis,[18] and also reversed endothelial dysfunction by improving the bioavailability nitric oxide.[19] Treatment with irbesartan significantly reduced the levels of inflammatory markers, including tumor necrosis factor-α receptor II, soluble vascular cell adhesion molecule-1 and superoxide, in normotensive patients with coronary artery disease.[20] Recent studies have demonstrated that statins may prevent angiotensin II-induced cellular and organ damage, such as the production of reactive oxygen species in vascular smooth muscle cells, cardiac hypertrophy and end-organ damage.[9][10]

ACE inhibitors improve the vascular reactivity and reduce the structural damage caused to hypercholesterolemic hypertensive subjects, and also reduce the morbidity and mortality in those with heart failure, as well as among survivors of a myocardial infarction.[21-23] The concept of cardiovascular protection due to ACE inhibition has recently been extended to high-risk patients with preserved ventricular function. In the Heart Outcomes Prevention Evaluation study, ramipril, administered for 4.5 years, resulted in lower rates of mortality, myocardial infarction and stroke among more than 9,000 patients at high risk of cardiovascular disease.[11]

Statins inhibit mevalonate synthesis, and are effective at reducing low density lipoprotein-cholesterol. As well as lowering lipids levels, statins have favorable effects on vascular inflammation,[24] endothelial function,[25] platelet adhesion and thrombosis,[26] and promote atherosclerotic plaque stabilization via the inhibition of inflammatory macrophages, depletion of the lipid core and strengthening of the fibrous cap. Statins are now recognized as anti-inflammatory agents, which downregulate inflammatory cytokines and C-reactive protein.[27]

There is a strong rationale for combining either an ARB or ACE inhibitor with a statin.[28-30] Horiuchi et al.[28] demonstrated that a combination of low-dose valsartan and low-dose fluvastatin acted synergistically to attenuate neointimal formation at doses that when administered alone had no effect, and which were devoid of any effects on the blood pressure or cholesterol levels. Nazzaro et al.[29] demonstrated a significant additive effect on hypercholesterolemia, structural vascular damage, blood pressure and vascular resistance with the combination of enalapril and simvastatin.

ARBs share the same mechanism of action, but have different pharmacokinetic profiles, which may account for their potential differences in efficacy. Determining the ARB or ACE inhibitor dose equivalence from outcomes trials is particularly confusing due to the differing dose frequency, titration requirements and level of renal function in various studies on the disease-state. Differences in the duration of treatment, patient population and drug dosage in the present study might have exerted no differences due to the ARBs and statins and ACE inhibitors and statins combinations, which might have resulted in this confusion. In addition, the selected initial dose may have been chosen using different criteria; thus, resulting in noncomparable degrees of blockade of the renin-angiotensin system. At present, little data are available on combinations of ARBs with statins.[31][32] In the present study, the beneficial effects on the restenosis and repeat PCI rate, and the cardiovascular events with the combination therapy of ARBs and simvastatin was compared with that of ACE inhibitors and simvastatin in patients having undergone PCI for ACS. In our study, there were no significant differences in the late loss and MACE, including restenosis and repeat PCI. It was concluded that the combination therapy of ARBs and statin showed Moreno greater beneficial ef-

fects compared with that of ACE inhibitors and statins in patients with ACS having undergone PCI. However, this result may have been caused by a "class effect" (meaning that there is no difference among the ARBs or ACE inhibitors) or the small number of patients in our study population according to the use of individual drugs; thus, long-term randomized, large scaled, prospective studies will be required to assess whether these differences are really clinically relevant by examining specific end points.

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