Impact of Angiotensin Converting Enzyme Inhibitor versus Angiotensin Receptor Blocker on Incidence of New-Onset Diabetes Mellitus in Asians

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Purpose: Angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) are associated with a decreased incidence of new-onset diabetes mellitus (NODM). The aim of this study was to compare the protective effect of ACEI versus ARBs on NODM in an Asian population.

Materials and Methods: We investigated a total of 2817 patients who did not have diabetes mellitus from January 2004 to September 2009. To adjust for potential confounders, a propensity score matched (PSM) analysis was performed using a logistic regression model. The primary end-point was the cumulative incidence of NODM, which was defined as having a fasting blood glucose ≥126 mg/dL or HbA1c ≥6.5%. Multivariable cox-regression analysis was performed to determine the impact of ACEI versus ARB on the incidence of NODM.

Results: Mean follow-up duration was 1839±1019 days in all groups before baseline adjustment and 1864±1034 days in the PSM group. After PSM (C-statistics=0.731), a total 1024 patients (ACEI group, n=512 and ARB group, n=512) were enrolled for analysis and baseline characteristics were well balanced. After PSM, the cumulative incidence of NODM at 3 years was lower in the ACEI group than the ARB group (2.1% vs. 5.0%, p=0.012). In multivariate analysis, ACEI vs. ARB was an independent predictor of the lower incidence for NODM (odd ratio 0.37, confidence interval 0.17−0.79, p=0.010).

Conclusion: In the present study, compared with ARB, chronic ACEI administration appeared to be associated with a lower incidence of NODM in a series of Asian cardiovascular patients.

Key Words: Angiotensin converting enzyme inhibitor, angiotensin receptor blocker, diabetes mellitus

INTRODUCTION

The renin-angiotensin system (RAS) is activated in all insulin

resistant states, including type II diabetes mellitus and metabolic syndrome.[1] RAS is also activated in arterial hypertension or congestive heart failure (CHF), which are associated with insulin resistant states. Angiotensin II has been shown to increase hepatic glucose production, decrease insulin sensitivity, and contribute to insulin resistance.[2] Nevertheless, other components, such as aldosterone and renin, are also involved in insulin resistance.[3] Meta-analysis of 10 randomized controlled trials in 75950 patients with hypertension or CHF showed a 22% risk reduction of new onset diabetes mellitus (NODM) with angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blockers (ARB) therapy after a mean follow up of 4.5 years.[2] The mechanisms underlying this protective

effect appear to be complex and may involve improvements in both insulin sensitivity and insulin secretion.[2] However, there were limited data to compare the protective effect of ACEI versus ARB on development of NODM, particularly in an Asians populations. Therefore, the aim of this study was to compare the protective effect of ACEIs versus ARBs on NODM in an Asian population.

MATERIALS AND METHODS

Study population

A total of 2817 consecutive patients who visited the cardiovascular center of Korea University Guro Hospital (KUGH) were retrospectively enrolled using the electronic database of KUGH from January 2004 to February 2010. Finally, a total of 2817 eligible patients without a history of diabetes were analyzed. The patients had underwent glucose tolerance test. The patients had HbA1c ≤5.7% and a fasting glucose level ≤100 mg/dL. The study protocol was approved by the Institutional Review Board at Korea University Guro Hospital (#KUGH 13017). All of the patients had no history of diabetes mellitus, and the patients who had pre-diabetic disease, such as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), were excluded. All of the patients were aged over 18 years, and were prescribed ARB or ACEI for hypertension. The first prescription of the study drug within the study period was defined as the start of the study. The patients were divided into the two groups who had been treated with ACEI or ARBs (ACEI group, n=576 patients, ARB group, n=2241 patients). To adjust for potential confounders, a propensity score matched (PSM) analysis was performed using the logistic regression model (C-statics=0.731). After PSM, a total of 1024 patients were enrolled for this analysis (ACEI group, n=512 patients, ARB group, n=512 patients).

Study definition and end-points

NODM was defined as a fasting blood glucose ≥126 mg/dL or HbA1c ≥6.5%.[4] The primary study end point was the cumulative incidence of NODM during a three-year clinical follow up. The secondary end points were clinical outcomes including total death, cardiac death, myocardial infarction (MI), cerebrovascular accidents (CVA), and major adverse cerebrocardiovascular accidents (MACCE: death, MI, CVA) during the three-year clinical follow up. The mean follow-up duration was 1839±1019 days in all groups before baseline adjustment and 1864±1034 days in the PSM group.

Statistics

All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means±standard deviation and were compared using Student's t-test. Categorical data were expressed as percentages and were compared using chi-square statistics or Fisher's exact test. A p-value of 0.05 was considered statistically significant. To adjust for potential confounders, propensity score analysis was performed using the logistic regression model. We tested all available variables that could be of potential relevance: age, body mass index (BMI), gender (male), cardiovascular risk factors [hypertension, myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), coronary artery spasm, hyperlipidemia, heart failure, angina pectoris, chest pain, atrial fibrillation, cardiac arrhythmia], co-medication treatment [angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers (CCBs), beta blockers (BBs), diuretics, warfarin], and laboratory findings (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride). The logistic model by which the propensity score was estimated showed good predictive value (C-statistic=0.731). Patients with the ACEI group were then 1-to-1 matched to the patients with the ARB group according to propensity scores with the nearest available pair matching method. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 512 well-matched pairs. A two-tailed p-value of <0.05 was considered to be statistically significant. Various clinical outcomes at 3 years were estimated with the Kaplan-Meier method, and differences between groups were compared with the log-rank test. Also, multivariate cox-regression analysis adjusted with following variables was performed to determine the different impact of ACEI versus ARB on incidence of NODM. The following factors were co-analyzed in multivariable analysis: gender (male), age, BMI (≥30 kg/m^2), hypertension, cardiovascular disease, coronary spasm, hyperlipidemia, current smoking, ACEIs versus ARBs, CCB, BB, diuretics, nitrates, and statins.

RESULTS

In this study, all of the patients were prescribed ARB or ACEI due to hypertension. Among the patients, 59.9% patients (1688/2817) had a history of hypertension and 40.1% patients (1129/2817) were prescribed ARB or ACEI for the first time. Mean follow-up duration was 1839±1019 days in all groups before baseline adjustment and 1864±1034 days in PSM group. After PSM, a total of 1024 patients (ARB group=512 and control group=512) were enrolled for this analysis. Before baseline adjustment, clinical characteristics showed that male gender, history of cardiovascular disease, including MI and prior PTCA, cerebrovascular disease (CVD), history of smoking, and current smoking were higher in the ACEI group, compared with the ARB group. However, age, BMI, previous medical history of hypertension, hyperlipidemia, congestive heart failure, atrial fibrillation, and mean duration of RAS inhibitors were similar between the two groups (Table 1). Before

baseline adjustment, baseline laboratory findings showed that the levels of fasting glucose, HbA1c, lipid levels, creatinine levels, and high sensitive C-reactive protein (hs CRP) were higher in the ARB group than the ACEI group. Before baseline adjustment, previous medical treatment showed that the previous use of BB, nitrate, and statins were higher in the ACEI groups, compared with the ARB groups. However, after PSM, baseline clinical characteristics, laboratory findings, previous medical treatment were well balanced between the two groups. Before baseline adjustment, the cumulative incidence of NODM for up to the three years was higher in the ARB group than the ACEI group (Table 2). Further, clinical events up to the three years, including total death, myocardial

infarction, and MACCE, were higher in the ACEI group than the ARB groups (Table 2). After PSM, the cumulative incidence of NODM was also higher in the ARB group than the ACEI group. However, clinical events up to the three years were similar between the two groups (Table 2). Multivariate analysis was adjusted for gender (male), age, body mass index (≥ 30 kg/m^2), hypertension, cardiovascular disease, coronary spasm, hyperlipidemia, current smoking, ARBs, ACEIs, calcium channel blockers, beta blockers, diuretics, nitrate, and statins. In multivariate analysis, previous history of coronary artery spams, and the use of ARB vs. ACEI were independent predictors of the incidence of NODM (Table 3).

Kaplan-Meier curves for the cumulative probabilities of

Table 1. Baseline Clinical Characteristics before and after PSM

Variables, n (%)	Entire patients			Matched patients		
	ACEIs (n=576)	ARBs (n=2241)	*p* value	ACEIs (n=512)	ARBs (n=512)	*p* value
Baseline characteristics						
Gender (male)	433 (75.1)	1139 (50.8)	<0.001	370 (72.2)	374 (73.0)	0.779
Age, yr	57.9±12.9	58.2±12.1	0.570	57.8±13.2	57.8±12.2	0.971
Body mass index (kg/m²)	24.4±3.3	24.5±3.1	0.371	24.4±3.3	24.4±3.0	0.998
Previous medical history						
Hypertension	336 (58.3)	1352 (60.3)	0.383	303 (59.1)	298 (58.2)	0.751
Hyperlipidemia	118 (20.4)	489 (21.8)	0.487	101 (19.7)	88 (17.1)	0.295
Cardiovascular disease	202 (35.0)	329 (14.6)	<0.001	143 (27.9)	149 (29.1)	0.678
Myocardial infarction	92 (15.9)	64 (2.8)	<0.001	52 (10.1)	50 (9.7)	0.835
Prior PTCA	125 (21.7)	141 (6.2)	<0.001	79 (15.4)	86 (16.7)	0.552
Coronary spasm	26 (4.5)	98 (4.3)	0.883	24 (4.6)	27 (5.2)	0.667
Cerebrovascular accidents	60 (10.4)	316 (14.1)	0.020	55 (10.7)	54 (10.5)	0.919
Heart failure	33 (5.7)	128 (5.7)	0.987	32 (6.2)	23 (4.4)	0.212
Atrial fibrillation & arrhythmia	45 (7.8)	179 (7.9)	0.890	41 (8.0)	40 (7.8)	0.908
History of smoking	191 (33.1)	611 (27.2)	0.005	160 (31.2)	163 (31.8)	0.840
Current smoking	164 (28.4)	541 (24.1)	0.032	139 (27.1)	137 (26.7)	0.888
RAS inhibitor duration (days)	1838±1070	1839±1006	0.978	1841±1076	1886±992	0.480
Baseline laboratory findings						
Fasting glucose (mg/dL)	93.6±8.4	94.6±7.6	0.006	93.7±8.2	93.9±7.6	0.694
A1c (%)	5.5±0.2	5.5±0.2	0.007	5.5±0.2	5.5±0.2	0.974
Total cholesterol (mg/dL)	174±39	180±36	<0.001	174±38	172±39	0.573
Triglyceride (mg/dL)	130±77	142±105	0.014	131±78	128±78	0.500
HDL-C (mg/dL)	49±13	51±13	0.010	50±13	50±13	0.368
LDL-C (mg/dL)	108±35	112±33	0.006	108±33	106±35	0.605
Creatinine (mg/dL)	1.0±0.4	0.9±0.3	<0.001	1.0±0.4	1.0±0.3	0.492
hs CRP (mg/dL)	4.0±11.1	2.8±9.1	0.042	3.9±11.6	3.4±12.5	0.600
Previous medical treatment						
Beta blockers	222 (38.5)	504 (22.4)	<0.001	171 (33.3)	164 (32.0)	0.641
Calcium channel blocker	272 (47.2)	1025 (45.7)	0.524	254 (49.6)	270 (52.7)	0.317
Diuretics	173 (30.0)	1002 (44.7)	<0.001	170 (33.2)	185 (36.1)	0.325
Nitrates	201 (34.8)	456 (20.3)	<0.001	161 (31.4)	162 (31.6)	0.946
Statins	275 (47.7)	702 (31.3)	<0.002	222 (43.3)	230 (44.9)	0.615

PSM, propensity score matching; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PTCA, percutaneous transluminal coronary angioplasty; RAS, renin-angiotensin system; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs CRP, high sensitive C-reactive protein.
Values are mean±SD or n (%).

NODM are presented in Fig. 1. Before PSM, the cumulative incidence of NODM was significantly higher in the ARB group than the ACEI group (*p*=0.019). After PSM, the cumulative in-

cidence of NODM remained significantly higher in the ARB group than the ACEI group (*p*=0.012). Kaplan-Meier curves for cumulative incidence for MACCE are presented in Fig. 2.

Table 2. NODM and Clinical Outcomes up to 3 Years before and after PSM

Variables, n (%)	Entire patients			Matched patients		
	ACEIs (n=576)	ARBs (n=2241)	*p* value	ACEIs (n=512)	ARBs (n=512)	*p* value
New-onset diabetes	13 (2.2)	99 (4.4)	0.018	11 (2.1)	26 (5.0)	0.012
ACEIs	13/576 (2.2)			11/512 (2.1)		
Ramipril	7/263 (2.6)			6/234 (2.5)		
Perindopril	2/136 (1.4)			1/110 (0.9)		
Other ACEIs	4/177 (2.2)			4/168 (2.3)		
Cilazapril	3/60 (5.0)			3/57 (5.2)		
Imidapril	0/33 (0.0)			0/31 (0.0)		
Enalapril	0/28 (0.0)			0/28 (0.0)		
Moexipril	0/27 (0.0)			0/26 (0.0)		
Captopril	1/19 (5.2)			1/16 (6.2)		
Lisinopril	0/10 (0.0)			0/10 (0.0)		
ARBs		99/2241 (4.4)			26/512 (5.0)	
Telmisartan		12/296 (4.0)			3/106 (2.8)	
Candesartan		17/258 (6.5)			4/86 (4.6)	
Valsartan		20/401 (4.9)			7/97 (7.2)	
Losartan		18/398 (4.5)			3/79 (3.7)	
Irbesartan		18/525 (3.4)			5/67 (7.4)	
Eprosartan		10/298 (3.3)			5/59 (8.4)	
Clinical outcomes at 3yrs						
Total death	10 (1.7)	14 (0.6)	0.010	9 (1.7)	6 (1.1)	0.435
Cardiac death	5 (0.8)	7 (0.3)	0.068	4 (0.7)	3 (0.5)	1.000
Myocardial infarction	6 (1.0)	8 (0.3)	0.037	5 (0.9)	4 (0.7)	1.000
Cerebrovascular accidents	6 (1.0)	17 (0.7)	0.501	5 (0.9)	5 (0.9)	1.000
MACCE	16 (2.7)	30 (1.3)	0.015	14 (2.7)	12 (2.3)	0.691

PSM, propensity score matching; NODM, new-onset diabetes mellitus; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MACCE, major adverse cerebral-cardiovascular events.
Values are n (%).

Table 3. Multivariate Analysis for Predictors of NODM before and after PSM

Variables	Entire patients		Matched patients	
	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Gender (male)	1.08 (0.72–1.62)	0.700	0.74 (0.35–1.57)	0.439
Age, yr	1.02 (1.00–1.04)	0.006	1.03 (0.99–1.06)	0.068
BMI≥30 (kg/m²)	0.50 (0.16–1.50)	0.219	0.27 (0.03–2.42)	0.248
Hypertension	1.56 (1.02–2.39)	0.039	1.54 (0.72–3.28)	0.257
Cardiovascular disease	0.98 (0.57–1.68)	0.954	0.65 (0.26–1.61)	0.359
Coronary spasm	1.57 (0.65–3.77)	0.313	3.49 (1.05–11.5)	0.040
Hyperlipidemia	1.18 (0.75–1.85)	0.465	0.54 (0.18–1.63)	0.278
Current smoking	0.91 (0.54–1.55)	0.751	0.59 (0.22–1.58)	0.303
ACEIs vs. ARBs	0.45 (0.24–0.84)	0.013	0.37 (0.17–0.79)	0.010
CCBs	0.82 (0.55–1.21)	0.327	1.59 (0.77–3.27)	0.203
BBs	1.05 (0.68–1.64)	0.798	1.78 (0.86–3.69)	0.117
Diuretics	1.44 (0.96–2.17)	0.075	1.02 (0.47–2.20)	0.952
Nitrates	1.42 (0.89–2.28)	0.138	1.72 (0.75–3.95)	0.199
Statin	1.77 (1.16–2.70)	0.007	1.84 (0.86–3.93)	0.114

NODM, new-onset diabetes mellitus; PSM, propensity score matching; OR, odds ratio; CI, confidence interval; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta blocker.

Before PSM, the cumulative incidence for MACCE was significantly higher in the ACEI group than the ARB group (*p*=0.014). However, after PSM, the cumulative incidences for MACCE were similar between the two groups (*p*=0.682). Cox proportional hazards regression models showed that after PSM, the use of ACEI had a 46% risk reduction of NODM, compared with the use of ARB (hazard ratio 0.54, 95% confidence interval 0.29−0.99, *p*-value 0.049), and the use of ACEI had a 63% risk elevation for MACCE, compared with the use of ARB, al-though there was no statistically significant difference between the two groups (hazard ratio 1.63, 95% confidence interval 0.83−3.21, *p*-value 0.154).

DISCUSSION

Recent studies from Western populations suggest a possible reduction in NODM with using RAS inhibitors. However,
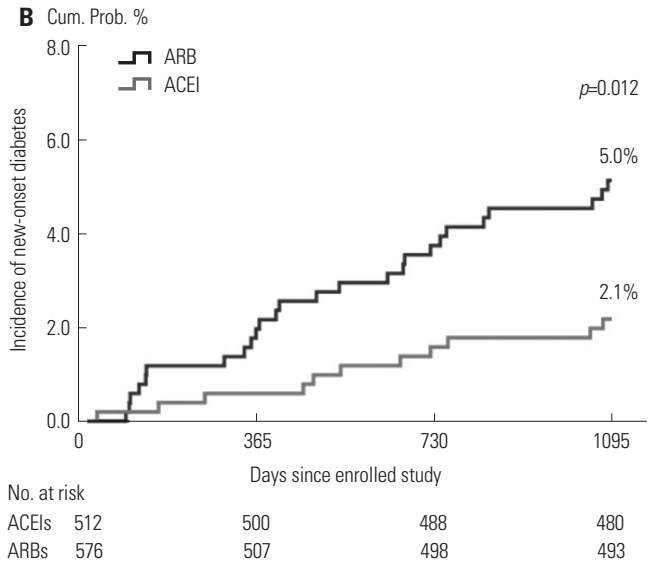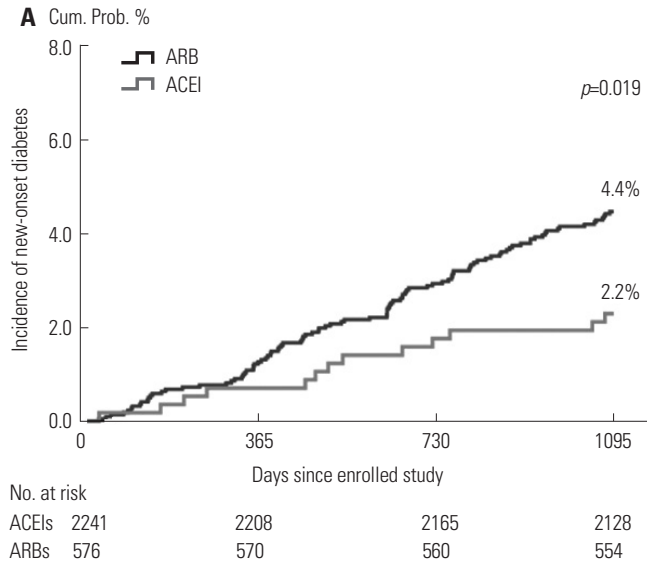

Fig. 1. Kaplan-Meier survival curves describing cumulative incidences of NODM in before and PSM. (A) Before PSM, Kaplan-Meier survival curves showed that the cumulative incidence of new-onset diabetes were significantly higher in the ARB group (black) than in the ACEI group (gray) (*p*=0.019, log-rank test). (B) After PSM, Kaplan-Meier survival curves showed that the cumulative incidence of new-onset diabetes were significantly higher in the ARB group (black) than in the ACEI group (gray) (*p*=0.012, log-rank test). NODM, new onset diabetes mellitus; PSM, propensity score matching; ARB, angiotensin II receptor blocker; ACEI, angiotensin converting enzyme inhibitor.
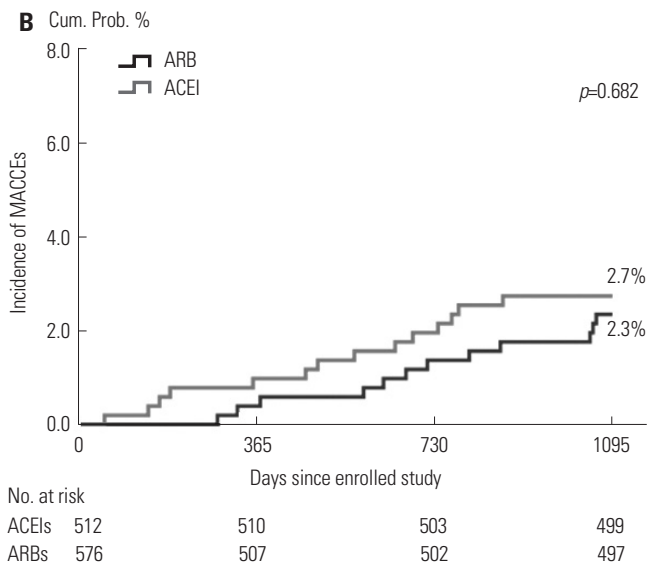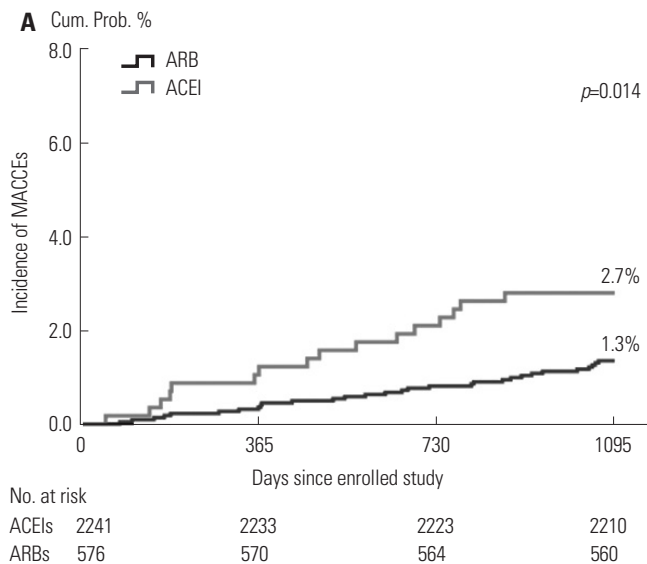

Fig. 2. Kaplan-Meier survival curves describing cumulative incidences of MACCE in before and PSM. (A) Before PSM, Kaplan-Meier survival curves showed that the cumulative incidence for MACCE were significantly higher in the ACEI group (gray) than in the ARB group (black) (*p*=0.014, log-rank test). (B) After PSM, Kaplan-Meier survival curves showed that the cumulative incidence for MACCE were similar between the ACEI group (gray) and the ARB group (black) (*p*=0.682, log-rank test). MACCE, major adverse cerebro-cardiovascular accidents; PSM, propensity score matching; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

whether these findings could be extended to Asian patients remains unclear. Furthermore, data are needed to ascertain whether there are effect differences between different types of RAS inhibitors. The present study addressed this interesting issue using data from a large-scale single center registry. The authors constructed two similar groups of patients using propensity score matching methods, which made possible comparisons of patients with ACEI versus with ARB.

Insulin resistance is a well-known risk factor for type 2 diabetes, cardiovascular disease, and metabolic syndrome. RAS contributes to the underlying pathophysiology of insulin resistance. Previous studies showed that blockade of RAS prevents insulin resistance and type 2 diabetes mellitus.[5,6] RAS blockade is known to improve blood circulation and cellular ionic balance, including potassium and magnesium, of skeletal muscle and pancreatic cells. As a result, RAS blockade improves peripheral insulin action, insulin secretion of pancreatic cell and prevent diabetes by promoting the recruitment and differentiation of adipocytes via A1 receptors.[7] However, there are different mechanisms for preventing insulin resistance between ACEIs and ARBs. ACEI works not only by inhibiting the conversion of angiotensin I to angiotensin II, but also by inhibiting the degradation of bradykinin. Therefore, ACEI allow the beneficial effects of nitric oxide and prostacycline, such as lowering blood pressure, and improving endothelial function. On the other hand, ARBs offer complete angiotensin II inhibition by interacting selectively with the receptor site, and thus, may result in accumulation of angiotensin II, which is the predominant renin angiotensin aldosteron system component contributing to insulin resistance.[6] Thus, ARB migh exert more stimuli for the incidence of NODM than ACEI, although the mechanisms should be investigated from different studies. Actually, the incidence of MACE was similar between the two groups after baseline adjustment, suggesting the possibility for two different mechanisms for ACEI and ARB did not result in clinical differences. In this study, the use of ACE reduced the incidence of NODM, but did not reduce the incidence of MACCE, compared to ARB. Therefore, the different mechanisms for preventing insulin resistance may be associated with different results of NODM. However, to get final results, a large scale multicenter study si needed.

In this study, clinical outcomes, including death, MI, and cerebro-cardiovascular events, up to 3 years were similar between teh two groups, suggesting similar protective effects for both drugs in preventing major cardiovascular hard endpoints. However, the cumulative incidence of NODM up to 3 years was higher in the ARB group than the ACEI group, and in Kaplan-Meyer curves, the incidence of NODM was higher in the ARB group than the ACEI group. Therefore, we suspect that ACEI may be more effective in preventing NODM than ARB, with a similar protective effect for cardiovascular events with ARB.

In this study, subgroup analysis of the ACEI group showed that the incidence of NODM seems to be numerically lower in the perindopril group, compared with the ramipril group and other ACEI groups (Table 2). Perindopril is a long acting, once-daily lipophilic ACEI with high tissue ACE affinity, which is associated with lowering angiotensin II and potentiating bradykinin, and may protect more efficiently against NODM than other usual ACEIs.[7]

A previous study in Sweden reported that the risk of NODM was lower in the candesartan group, compared with the enalapril group (hazard ratio 0.81, 95% confidence interval 0.69–0.96, p-value 0.01).[5] Our study results showed that the incidence of NODM was lower in the ACEI group than ARB group. When we consider our subgroup analysis results, the incidence of NODM by candesartan was relatively lower (4.6%) than other ARBs, and enalapril is an older ACEI than perindopril. Thus it may be difficult to see the differences between candesartan and enalapril with regard to the incidence of NODM.

In our study, subgroup analysis of ARB group showed that the incidence of NODM seems to be lower with telmisartan (2.8%), losartan (3.7%), and candesartan (4.6%), compared with valsartan (7.2%), irbesartan (7.4%), and eprosartan (8.4%) after adjustment (Table 2). Potent ARBs, such as telmisartan and candesartan, offer long lasting inhibition of angiotensin 1 receptor, which is associated with sustained blood pressure reduction and more efficient protection against NODM than other usual ARBs.[8]

In the JUPITER study, pre-diabetic disease was the most important risk factor for NODM in patients receiving long-term statin treatment.[9] Therefore, in this study, pre-diabetic disease, such as IGT and IFG, was not co-analyzed with the other risk factors in multivariable analysis regarding the independent predictors of NODM, because pre-diabetic disease is strong bias of results. In this study, hyperlipidemia, as well as the use of statins and beta-blockers, were not independent risk factors for NODM, because the patients in this study had less cardiovascular risk factors, metabolic syndrome components, and less diabetogenic as compared with previous studies to get more clear messages from the analysis.

In this study, there were several limitations. First, we analyzed patients taking ACEI or ARB for more than three months continuously. However, there were no data about the treatment gaps/stops and the compliance during the 3-years follow up in the present study. However, we could easily identify drug intolerance, such as dry cough due to ACEI after the 3 months prescription, and in general, once a patient is comfortable with either ACEI or ARB, most physicians should have maintained their use for more a prolonged time period. We excluded crossover cases within short time period due to drug intolerance to exclude bias. Second, we could not include more detailed risk factors of atherosclerosis, such as family history, abdominal circumference, and socio-econom-

ic status. Although this can be a limitation, the rest of other factors will indirectly reflect on the possible missing variables.

In conclusion, RAS inhibitors are known to be effective in preventing NODM. However, there may be different mechanisms of RAS inhibition between ACEI and ARB. In this study, after the PSM analysis, the cumulative incidence of NODM up to 3 years was lower in the ACEI group than the AEB group. Similarly, in Kaplan-Meyer curves, the incidence of NODM was lower in the ACEI group than the ARB group. Therefore, we assumed that ACEI might be more effective in preventing NODM than ARB, with similar protective effects for major cardiovascular events. Nevertheless, larger clinical trial would be needed to identify the difference between ACEI and ARB in preventing NODM and clinical events.

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