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Calcium channel blocker monotherapy versus combination with renin-angiotensin system inhibitors on the development of new-onset diabetes mellitus in hypertensive Korean patients

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Abstract

Background In real practice, two or more antihypertensive drugs are needed to achieve target blood pressure. We investigated the comparative beneficial actions of combination therapy of renin-angiotensin system inhibitors (RASI), with calcium channel blockers (CCB) over CCB monotherapy on the development of new-onset diabetes mellitus (NODM) in Korean patients during four-year follow-up periods. **Methods** A total of 3208 consecutive hypertensive patients without a history of diabetes mellitus who had been prescribed CCB were retrospectively enrolled from January 2004 to December 2012. These patients were divided into the two groups according to the additional use of RASI (the RASI group, n = 1221 and the no RASI group, n = 1987). Primary endpoint was NODM, defined as a fasting blood glucose ≥ 126 mg/dL or hemoglobin A1c ≥ 6.5%. Secondary endpoint was major adverse cardiac events (MACE) defined as total death, myocardial infarction (MI) and percutaneous coronary intervention (PCI). **Results** After propensity score-matched (PSM) analysis, two propensity-matched groups (939 pairs, n = 1878, C-statistic = 0.743) were generated. The incidences of NODM (HR = 1.009, 95% CI: 0.700–1.452, P = 0.962), MACE (HR = 0.877, 95% CI: 0.544–1.413, P = 0.589), total death, MI, PCI were similar between the two groups after PSM during four years. **Conclusions** The use of RASI in addition to CCB showed comparable incidences of NODM and MACE compared to CCB monotherapy in non-diabetic hypertensive Korean patients during four-year follow-up period. However, large-scaled randomized controlled clinical trials will be required for a more definitive conclusion.

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Keywords: Calcium channel blocker; Diabetes mellitus; Renin-angiotensin system inhibitors

1 Introduction

Arterial hypertension and diabetes mellitus (DM) are well known important risk factors of cardiovascular diseases (CVD) and often these disease entities have intimate relationships with each other.[1–3] According to a previous study the development of type 2 DM (T2DM) was about 2.5 times higher in hypertensive patients compared to normotensive patients.[4] In patients with T2DM, the incidence of CVD is about two- and four-times higher than the general population.[5] Therefore, hypertensive patients have a relatively higher risk of new-onset DM (NODM) and this may trigger further cardiovascular diseases.[6] Antihypertensive drug

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impacts on the blood glucose level are diverse according to the class of those drugs.[7–9] Among the antihypertensive drugs, the incidence of NODM is unchanged or increased by thiazide diuretics and beta-blockers (BB)[10,11] and unchanged or decreased by calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB).[12,13] Grimm, *et al*.[14] also reported that diuretics and BB can increase the incidence of NODM, but ARB as well as ACEI has a preventive effect and CCB has a neutral position in the development of NODM. Further, they also suggested these effects are much stronger when both substance classes are used in combination. In addition, Burke, *et al*.[15] reported antihypertensive drugs combination therapy including ACEI had lowered the risk of NODM more than antihypertensive drug combinations without an ACEI. But other meta-analysis demonstrated the risk of NODM was lower in patients treated ARB compared with ACEI.[16] There are rare studies[17] on the relationship between antihypertensive therapies and the incidence of NODM in hypertensive Asian patients especially, in Korean population. The purpose of this study was to investigate the comparative efficacy of combination therapy of renin-angiotensin system inhibitors (RASI) which include ACEI or ARB, with CCB over CCB monotherapy on the development of NODM during four-year follow-up period in non-diabetic hypertensive Korean patients.

2 Methods

2.1 Study population

This study was a non-randomized, single center, observational and retrospective study. Finally, a total of 3208 consecutive hypertensive patients without a history of DM who had been prescribed CCB were retrospectively enrolled using the electronic database of Korea University Guro Hospital from January 2004 to December 2012. All enrolled patients had undergone a glucose tolerance test. Inclusion criteria were both hemoglobin (Hb) A1c ≤ 5.7% and a fasting glucose level ≤ 100 mg/dL and the exclusion criteria were the patients who had pre-diabetic disease, such as impaired glucose tolerance and impaired fasting glucose. The first prescription day within the study period was defined as the start day of the study. A total of 3208 hypertensive patients were divided into the two groups according to the additional use of RASI (RASI use group, n = 1221 and no use group, n = 1987) to CCB. The RASI use group was composed with ACEI prescribed patients (n = 255) or ARB prescribed patients (n = 966). To adjust for potential confounders, a propensity score-matched (PSM) analysis was performed using the logistic regression model (C-statics = 0.743). After PSM, 939 well-matched pairs (n = 1878) were generated and, the baseline characteristics of the two groups were balanced (Table 1).

2.2 Study definitions and study endpoints

NODM was defined as fasting blood glucose (FBG) ≥ 126 mg/dL or HbA1c ≥ 6.5%.[18] The primary study endpoint was the cumulative incidence of NODM during a four-year clinical follow-up periods. The secondary endpoints was major adverse cardiac events (MACE) defined as total death, myocardial infarction (MI) and percutaneous coronary intervention (PCI). The mean follow-up duration was 1825 ± 1221 days in all groups before baseline adjustment and 1825 ± 1268 days in the PSM group. The mean prescription duration of the RASI group (CCB with RASI) was 1564 ± 1007 days and the no RASI group (CCB monotherapy) was 1689 ± 1040 days in all patients. After PSM, the mean prescription duration of the CCB with RASI group was 1568 ± 1016 days and the CCB group was 1796 ± 1043 days. We followed up on the clinical data of all enrolled patients through face-to-face interviews at outpatient clinics, medical chart reviews and telephone calls.

2.3 Statistical analysis

For continuous variables, differences between the two groups were evaluated with the unpaired t-test or the Mann-Whitney rank test. Data were expressed as mean ± SD. For discrete variables, differences were expressed as counts and percentages and analyzed with χ^2 or Fisher's exact test between the groups as appropriate. To adjust for potential confounders, PSM analysis was performed using the logistic regression model. All data were processed with the Statistical Package for the Social Sciences version 20.0 (IBM, Armonk, NY, USA). We tested all available variables that could be of potential relevance: gender, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, previous PCI, previous cerebrovascular accident (CVA), previous heart failure (HF), coronary artery spasm, atrial fibrillation and arrhythmia, current smokers, current alcoholics, laboratory findings [FBG, HbA1c, total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein-cholesterol, high-sensitivity C-reactive protein, Hb, serum creatinine] and medications (BB, diuretic, nitrate, lipid lowering agents, aspirin, clopidogrel, cilostazole). The logistic model by which the propensity score was estimated showed good a predictive value (C-statistic = 0.743). Patients with the CCB with RASI group were then one-to-one matched to the patients with the CCB group according to propensity

Table 1. Baseline clinical characteristics and laboratory results.

Variables	Entire patients			Propensity score-matched patients		
	CCB + RASI (*n* = 1221)	CCB (*n* = 1987)	*P*-value	CCB + RASI (*n* = 939)	CCB (*n* = 939)	*P*-value
Gender, men	660 (54.1%)	926 (46.6%)	< 0.001	487 (51.9%)	502 (53.5%)	0.488
Age, yrs	59.0 ± 11.9	58.3 ± 11.7	0.088	59.2 ± 11.8	59.4 ± 12.0	0.749
Body mass index, kg/m^2	24.9 ± 3.2	24.8 ± 3.2	0.323	24.8 ± 3.1	25.0 ± 3.2	0.421
Systolic blood pressure, mmHg	137.8 ± 21.1	134.1 ± 20.0	< 0.001	137.5 ± 20.9	135.8 ± 19.7	0.182
Diastolic blood pressure, mmHg	84.7 ± 13.9	82.2 ± 12.8	< 0.001	83.8 ± 13.7	83.0 ± 13.2	0.311
Heart rate, beats/minute	75.5 ± 13.2	74.9 ± 12.4	0.366	75.7 ± 13.4	75.4 ± 12.4	0.718
Previous PCI	151 (12.4%)	141 (7.1%)	< 0.001	119 (12.7%)	100 (10.6%)	0.172
Previous cerebrovascular accident	186 (15.2%)	292 (14.7%)	0.678	140 (14.9%)	131 (14.0%)	0.555
Previous heart failure	75 (6.1%)	102 (5.1%)	0.224	54 (5.8%)	61 (6.5%)	0.500
Dyslipidemia	117 (9.6%)	125 (6.3%)	0.001	85 (9.1%)	75 (8.0%)	0.457
Coronary artery spasm	35 (2.9%)	75 (3.8%)	0.170	29 (3.1%)	26 (2.8%)	0.681
Atrial fibrillation & arrhythmia	68 (5.6%)	106 (5.3%)	0.776	52 (5.5%)	52 (5.5%)	1.000
Current smokers	277 (22.7%)	446 (22.4%)	0.840	215 (22.9%)	212 (22.6%)	0.783
Current alcoholics	428 (35.1%)	639 (32.2%)	0.029	324 (34.5%)	316 (33.7%)	0.238
Fasting blood glucose, mg/dL	95.3 ± 7.9	94.5 ± 8.0	0.006	95.1 ± 7.8	95.1 ± 8.0	0.955
Hemoglobin A1c	5.62% ± 0.28%	5.58% ± 0.29%	< 0.001	5.60% ± 0.29%	5.60% ± 0.27%	0.640
Total cholesterol, mg/dL	179.4 ± 36.7	180.5 ± 35.6	0.421	178.2 ± 36.7	179.4 ± 35.5	0.477
Triglyceride, mg/dL	144.8 ± 93.5	130.1 ± 94.6	< 0.001	138.0 ± 79.3	136.2 ± 104.1	0.678
HDL cholesterol, mg/dL	50.3 ± 12.9.	51.7 ± 13.5	0.006	50.3 ± 12.6	50.6 ± 13.1	0.596
LDL cholesterol, mg/dL	113.4 ± 33.5	114.2 ± 32.9	0.559	112.7 ± 33.4	114.3 ± 33.4	0.339
High sensitivity CRP, mg/dL	3.1 ± 10.1	2.4 ± 10.4	0.123	2.8 ± 7.2	2.9 ± 13.2	0.731
Hemoglobin, mg/dL	13.9 ± 1.7	13.7 ± 1.5	0.003	13.8 ± 1.7	13.8 ± 1.5	0.890
Serum creatinine, mg/dL	0.9 ± 0.6	0.8 ± 0.2	< 0.001	0.8 ± 0.6	0.8 ± 0.2	0.720
Medications						
Beta-blockers	339 (27.8%)	344 (17.3%)	< 0.001	234 (24.9%)	239 (25.4%)	0.790
Diuretics	572 (46.8%)	316 (15.9%)	< 0.001	306 (32.5%)	302 (32.1%)	0.844
Nitrates	338 (27.7%)	834 (42.0%)	< 0.001	290 (30.8%)	294 (31.3%)	0.842
Lipid lowering agents	483 (39.6%)	698 (35.1%)	0.012	384 (40.8%)	384 (40.8%)	1.000
Aspirin	28 (2.3%)	23 (1.2%)	0.013	19 (2.0%)	17 (1.8%)	0.736
Clopidogrel	260 (21.3%)	289 (14.5%)	< 0.001	196 (20.8%)	193 (20.5%)	0.864
Cilostazole	66 (5.4%)	79 (4.0%)	0.058	52 (5.5%)	50 (5.3%)	0.839
ACEI	255 (20.9%)			209 (22.3%)		
Ramipril	135 (11.1%)			104 (11.1%)		
Perindopril	54 (4.4%)			49 (5.2%)		
Cilazapril	22 (1.8%)			17 (1.8%)		
Imidapril	19 (1.6%)			18 (1.9%)		
Moexipril	10 (0.8%)			8 (0.9%)		
Enalapril	9 (0.7%)			8 (0.9%)		
Captopril	6 (0.5%)			5 (0.5%)		
ARB	966 (79.1%)			730 (77.7%)		
Losartan	223 (18.3%)			171 (18.2%)		
Irbesartan	167 (13.6%)			123 (13.1%)		
Valsartan	159 (13.0%)			101 (10.7%)		
Telmisartan	107 (8.8%)			73 (7.8%)		
Olmesartan	107 (8.8%)			87 (9.3%)		
Candesartan	104 (8.5%)			87 (9.3%)		
Eprosartan	94 (7.7%)			84 (8.9%)		
Fimasartan	5 (0.4%)			4 (0.4%)		
Prescription duration, days	1564 ± 1007	1689 ± 1040	0.157	1568 ± 1016	1796 ± 1043	0.102

Data are presented as means ± SD or *n* (%). The *P*-values for continuous data and categorical data were obtained from analysis of variance and chi-square test. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PCI: percutaneous coronary intervention; RASI: renin-angiotensin system inhibitor.

scores with the nearest available pair matching method. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 939 well-matched pairs. For all analyses, a two-tailed *P*-value of < 0.05 was considered to be statistically significant. Various clinical outcomes at four-year were estimated with the Kaplan-Meier method, and differences between groups were compared with the log-rank test. In addition, multivariate Cox-regression analysis adjusted with the following variables was performed to determine the different impact of CCB with RASI versus CCB on the incidence of NODM. The following factors were co-analyzed in multivariate Cox-regression analysis: CCB with RASI *vs*. CCB, age (≥ 65 years), gender (men), BMI (≥ 24 kg/m^2), SBP, DBP, dyslipidemia, previous PCI, previous CVA, previous HF, current smokers, current alcoholics, triglyceride, FBG, serum creatinine, BB, diuretics, nitrates and lipid lowering agents.

3 Results

A total of 3028 eligible hypertensive patients who prescribed CCB were finally enrolled for the analysis. After PSM analysis, 939 matched pairs (n = 1878) were generated and their baseline characteristics, laboratory findings, and medication history are summarized in Table 1. In the unmatched population, men, SBP, DBP, previous history of PCI, current alcoholics, FBG, HbA1c, triglyceride, Hb, serum creatinine and the prescription rates of BB, diuretics, lipid lowering agents, aspirin, and clopidogrel were significantly higher in CCB with RASI use group. The level of HDL-cholesterol and the use of nitrates were significantly higher in the CCB group. After PSM these differences were balanced. In the unmatched population, the use of ACEI was 20.9% (255/1221) and ARB 79.1% (966/1221). After PSM, ACEI was 22.3% (209/939) and ARB was 77.7% (730/939). Among the RASI drugs, ramipril was the most frequently prescribed ACEI before [135/1221 (11.1%)] and after PSM [104/939 (11.1%)] and Losartan was the ARB [223/1221 (18.3%) *vs*. 171/939 (18.2%)]. The total prescription duration of each drug between the two groups was not significantly different before and after PSM (Table 1).

Table 2 and Figure 1 show the clinical outcomes by Kaplan-Meier curved analysis and Cox-proportional hazard analysis at four years. In the unmatched population, the incidences of NODM (8.6% *vs*. 6.8%, Log rank P = 0.149) were not statistically different between the two groups. However, the incidence of MACE (5.2% *vs*. 3.3%, Log rank P = 0.033), total death (1.2% *vs*. 0.3%, Log rank P = 0.003) and cardiac death (0.7% *vs*. 0.1%, Log rank P = 0.020) were significantly higher in the CCB with RASI group. After PSM, the incidences of NODM [8.5% *vs*. 8.3%, Log rank P = 0.962, hazard ratio (HR) = 1.009, 95% confidence interval

Table 2. Clinical outcomes by Kaplan-Meier curved analysis and Cox-proportional hazard ratio analysis at four years.

Outcomes	Cumulative events at four years			HR (95% CI)	*P*-value
	CCB + RASI	CCB	Log rank		
Primary end point					
New-onset diabetes mellitus	81 (8.6%)	93 (6.8%)	0.149	0.803 (0.596–1.082)	0.150
Secondary end points					
MACE	52 (5.2%)	50 (3.3%)	0.033	0.657 (0.445–0.968)	0.034
Total death	12 (1.2%)	3 (0.3%)	0.003	0.178 (0.050–0.631)	0.008
Cardiac death	6 (0.7%)	1 (0.1%)	0.020	0.121 (0.015–1.009)	0.051
Myocardial infarction	9 (0.9%)	5 (0.3%)	0.072	0.381 (0.128–1.137)	0.084
Percutaneous coronary intervention	42 (3.4%)	48 (2.4%)	0.089	0.700 (0.462–1.059)	0.091
Propensity score-matched patients					
Primary end point					
New-onset diabetes mellitus	59 (8.5%)	56 (8.3%)	0.962	1.009 (0.700–1.452)	0.962
Secondary end point					
MACE	37 (4.8%)	31 (4.3%)	0.589	0.877 (0.544–1.413)	0.589
Total death	7 (0.9%)	3 (0.5%)	0.241	0.454 (0.117–1.757)	0.253
Cardiac death	2 (0.3%)	1 (0.1%)	0.606	0.537 (0.049–5.918)	0.611
Myocardial infarction	6 (0.9%)	2 (0.3%)	0.178	0.350 (0.071–1.734)	0.198
Percutaneous coronary intervention	30 (3.2%)	29 (3.1%)	0.895	0.966 (0.580–1.610)	0.895

Data are presented as n (%) unless other indicated. CCB: calcium channel blocker; HR: hazard ratio; MACE: major adverse cardiac event; RASI: renin-angiotensin system inhibitor.

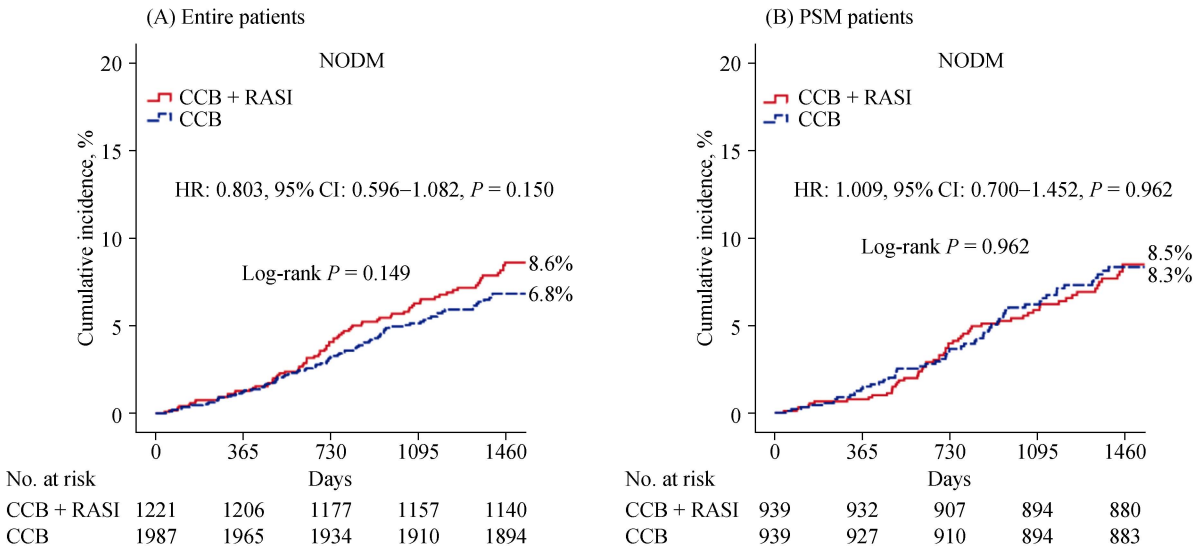

Figure 1. Kaplan-Meier curved analysis for NODM in entire patients (A) and PSM patients (B) at four years. CCB: calcium channel blocker; HR: hazard ratio; NODM: new-onset diabetes mellitus; PSM: propensity score-matched; RASI: renin-angiotensin system inhibitor.

(CI): 0.700–1.452, P = 0.962] and MACE (4.8% *vs*. 4.3%, Log rank P = 0.589, HR = 0.877, 95% CI: 0.544–1.413, P = 0.589) were similar between the two groups. In addition, the incidences of total death (0.9% *vs*. 0.5%, Log rank P = 0.241), cardiac death (0.3% *vs*. 0.1%, Log rank P = 0.606), MI (0.9% *vs*. 0.3%, Log rank P = 0.178) and PCI (3.2% *vs*. 3.1%, P = 0.895) were also similar between the two groups. In Table 3, the incidence of NODM was not significantly associated with specific types of drugs among RASI after PSM. Table 4 shows independent predictors of NODM before and after PSM. In the entire patients, the previous PCI history was a significant predictor for NODM before (HR = 0.639; 95% CI: 0.416–0.984; P = 0.042) and after adjustment (HR = 0.413; 95% CI: 1.175–0.976; P = 0.044). However, after PSM, there were no significant predictors for NODM in this study. Subgroup analysis for NODM in PSM patients shows similar results (Figure 2). Figure 3 shows subgroup analysis for NODM in PSM patients.

Table 3. The cumulative events of new-onset diabetes mellitus between ACEI and ARB at four years.

Variables	Entire patients			PSM patients		
	Events	HR (95% CI)	*P*-value	Events	HR (95% CI)	*P*-value
ACEI	15/255 (5.9%)	1.056 (0.612–1.824)	0.844	12 /209 (5.7%)	1.223 (0.657–2.276)	0.525
Ramipril	7/135 (5.2%)	1.230 (0.578–2.621)	0.591	4/104 (3.8%)	1.928 (0.711–5.225)	0.197
Perindopril	4/54 (7.4%)	0.708 (0.263–1.909)	0.495	4/49 (8.2%)	0.693 (0.255–1.877)	0.470
Cilazapril	1/22 (4.5%)	1.409 (0.197–10.06)	0.732	1/17 (5.9%)	1.172 (0.164–8.390)	0.875
Imidapril	1/19 (5.3%)	0.886 (0.124–6.324)	0.904	1/18 (5.6%)	0.893 (0.125–6.397)	0.911
Moexipril	1/10 (10%)	0.388 (0.054–2.769)	0.345	1/8 (12.5%)	0.300 (0.042–2.160)	0.231
Enalapril	0/9 (0.0%)	-	-	0/8 (0.0%)	-	-
Captopril	1/6 (16.7%)	0.321 (0.045–2.290)	0.257	1/5 (20.0%)	0.260 (0.036–1.865)	0.180
ARB	66/966 (6.8%)	0.795 (0.587–1.078)	0.140	47/730 (6.4%)	0.969 (0.671–1.401)	0.869
Losartan	19/223 (8.5%)	0.665 (0.413–1.071)	0.093	15/171 (8.8%)	0.700 (0.407–1.204)	0.198
Irbesartan	8/167 (5.0%)	1.334 (0.656–2.712)	0.426	4/123 (3.3%)	2.209 (0.815–5.987)	0.119
Valsartan	12/159 (7.5%)	0.795 (0.442–1.429)	0.443	7/101 (6.9%)	0.955 (0.445–2.051)	0.906
Telmisartan	8/107 (7.5%)	0.742 (0.365–1.508)	0.410	6/73 (8.2%)	0.591 (0.275–1.268)	0.177
Olmesartan	6/107 (5.6%)	0.903 (0.424–1.923)	0.791	5/87 (5.7%)	1.085 (0.443–2.658)	0.858
Candesartan	11/104 (10.6%)	0.469 (0.261–0.842)	0.011	8/87 (9.2%)	0.556 (0.282–1.098)	0.091
Eprosartan	1/94 (1.1%)	5.431 (0.761–38.77)	0.092	1/84 (1.2%)	5.550 (0.775–39.74)	0.088
Fimasartan	1/5 (20.0%)	0.243 (0.043–2.214)	0.243	1/4 (25.0%)	0.279 (0.039–2.000)	0.204

Data are presented as *n* (%) unless other indicated. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; HR: hazard ratio; PSM: propensity score-matched.

Table 4. Independent predictors of new-onset diabetes mellitus before and after PSM.

Variables	Entire patients				PSM patients			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CCB + RASI *vs.* CCB	0.822 (0.611–1.105)	0.194	0.960 (0.532–1.732)	0.892	1.046 (0.728–1.501)	0.810	1.077 (0.535–2.166)	0.836
Age ≥ 65 years	0.610 (0.453–0.823)	0.001	1.162 (0.620–2.178)	0.639	0.632 (0.439–0.911)	0.014	1.136 (0.514–2.509)	0.753
Gender, men	0.899 (0.669–1.207)	0.478	0.948 (0.484–1.857)	0.876	1.258 (0.874–1.810)	0.217	1.316 (0.527–3.287)	0.556
BMI ≥ 24 kg/m^2	1.194 (0.830–1.717)	0.339	1.250 (0.723–2.164)	0.424	1.136 (0.724–1.784)	0.579	1.373 (0.667–2.827)	0.389
Systolic blood pressure	1.000 (0.990–1.010)	0.991	0.989 (0.981–1.018)	0.958	0.997 (0.984–1.010)	0.651	0.997 (0.972–1.022)	0.807
Diastolic blood pressure	0.997 (0.981–1.013)	0.718	0.998 (0.968–1.029)	0.902	0.993 (0.973–1.014)	0.519	1.001 (0.963–1.041)	0.954
Dyslipidemia	0.803 (0.480–1.342)	0.402	0.613 (0.270–1.391)	0.242	1.059 (0.536–2.090)	0.869	0.762 (0.246–2.358)	0.637
Previous PCI	0.639 (0.416–0.984)	0.042	0.413 (0.175–0.976)	0.044	0.633 (0.391–1.025)	0.063	0.288 (0.096–0.861)	0.056
Previous CVA	0.614 (0.430–0.877)	0.007	0.782 (0.332–1.843)	0.574	0.623 (0.400–0.970)	0.036	0.526 (0.198–1.398)	0.198
Previous heart failure	0.747 (0.416–1.343)	0.330	0.043 (0.189–1.042)	0.062	0.700 (0.354–1.381)	0.303	0.428 (0.153–1.195)	0.105
Current smokers	0.841 (0.591–1.196)	0.335	0.728 (0.375–1.410)	0.346	0.844 (0.548–1.302)	0.444	0.500 (0.209–1.194)	0.119
Current alcoholics	0.920 (0.665–1.271)	0.612	0.976 (0.514–1.853)	0.941	0.933 (0.626–1.389)	0.731	1.306 (0.540–3.155)	0.553
Triglyceride	1.001 (1.000–1.003)	0.033	1.001 (0.999–1.003)	0.205	0.999 (0.996–1.004)	0.120	1.001 (0.998–1.004)	0.452
Fasting blood glucose	1.038 (1.018–1.058)	< 0.001	1.025 (0.987–1.064)	0.196	1.039 (1.014–1.064)	0.002	1.052 (0.999–1.109)	0.056
Serum creatinine	1.119 (0.825–1.517)	0.470	0.498 (0.103–2.401)	0.385	0.939 (0.523–1.686)	0.834	0.340 (0.036–3.224)	0.347
Beta blockers	0.704 (0.512–0.968)	0.031	0.778 (0.417–1.450)	0.429	0.856 (0.578–1.261)	0.426	1.284 (0.554–2.978)	0.560
Diuretics	1.331 (0.981–1.807)	0.066	1.558 (0.826–2.937)	0.171	1.250 (0.864–1.809)	0.237	1.409 (0.642–3.090)	0.392
Nitrates	0.819 (0.607–1.104)	0.190	0.758 (0.422–1.360)	0.353	0.761 (0.525–1.103)	0.149	0.769 (0.337–1.754)	0.532
Lipid lowering agents	0.702 (0.522–0.944)	0.019	1.121 (0.599–1.732)	0.721	0.833 (0.579–1.199)	0.325	1.502 (0.619–3.646)	0.368

BMI: body mass index; CCB: calcium channel blocker; CVA: cerebrovascular accident; HR: hazard ratio; PCI: percutaneous coronary intervention; PSM: propensity score-matched; RASI: renin-angiotensin system inhibitor.

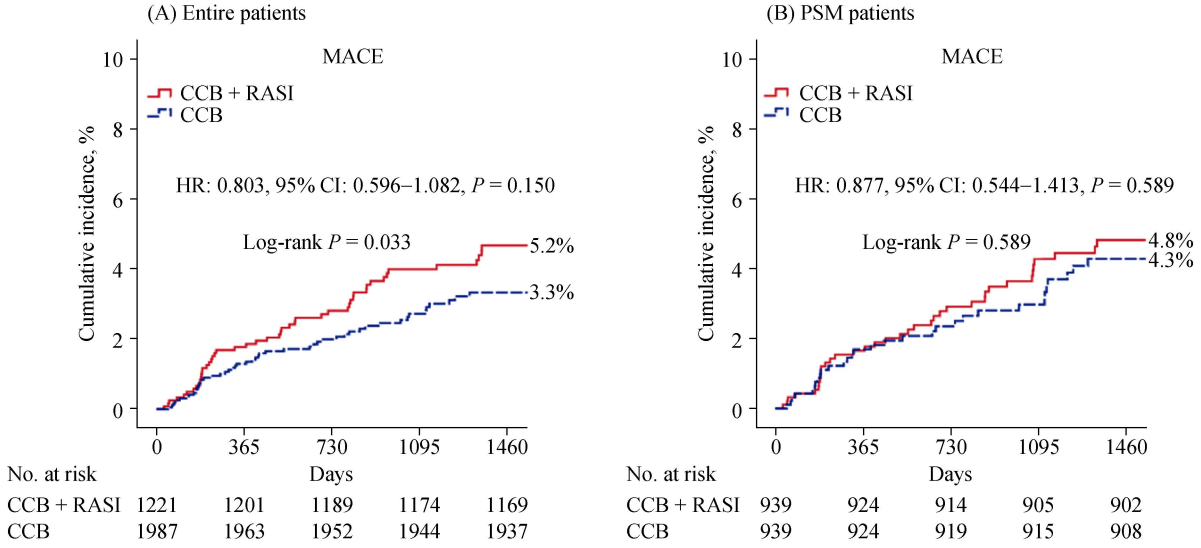

Figure 2. Kaplan-Meier curved analysis for MACE in entire patients (A) and PSM patients (B) at four years. CCB: calcium channel blocker; HR: hazard ratio; MACE: major adverse cardiac event; PSM: propensity score-matched; RASI: renin-angiotensin system inhibitor.

4 Discussion

The main findings of this study were: (1) the development of NODM was not significantly different between the two groups (CCB with RASI group *vs*. CCB group) and (2) the incidences of MACE, total death, MI, PCI were also similar between the two groups in non-diabetic hypertensive Korean patients during four-year follow-up period.

One of important features of this study was that many

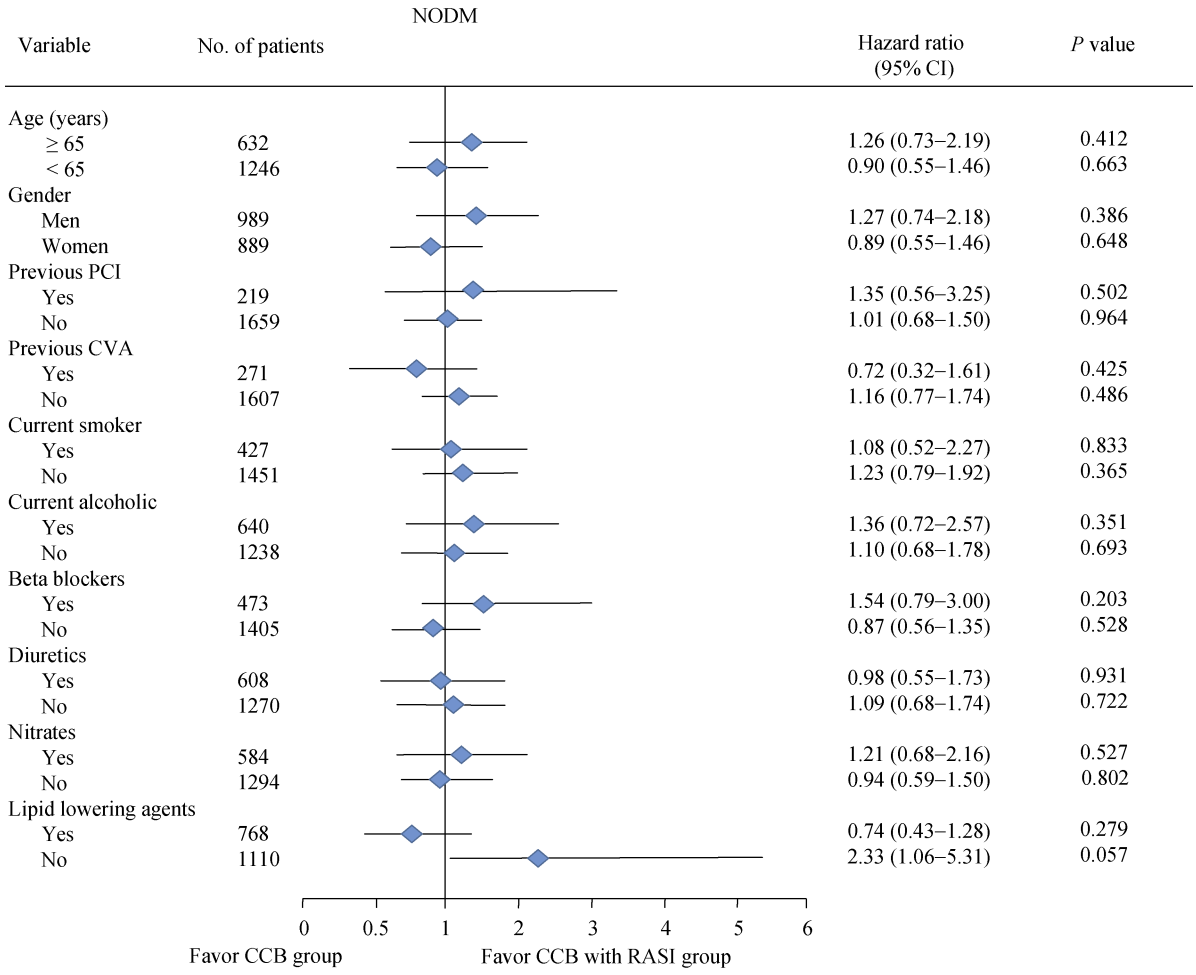

Figure 3. Subgroup analysis for NODM in PSM patients. CCB: calcium channel blocker; CVA: cerebrovascular accident; NODM: new-onset diabetes mellitus; PCI: percutaneous coronary intervention; PSM: propensity score-matched; RASI: renin-angiotensin system inhibitor.

previous reports[10–14] which showed the positive cause-effect relationship between antihypertensive drugs and NODM could be extended to hypertensive Asian patients, especially Korean patients.

Several previous guidelines recommended CCB as one of the first-line drugs suitable for the beginning and maintenance of their antihypertensive role in hypertensive patients.[19,20] In most patients, two or more antihypertensive drugs are needed to achieve target blood pressure and recent guidelines recommend combination therapy to control blood pressure levels.[19–21] Therefore, the baseline study population of this study was composed of patients whom had been prescribed CCB to control their blood pressure, in addition, this inclusion was based on the premise that CCB may be associated with reduced possibility of NODM compared with diuretics and BB.[10] Because there is some debate[15–17,22] about the comparative superiority of beneficial effects between ACEI and ARB on the incidence of NODM in hypertensive patients, we considered these two drugs, ACEI and ARB, as a one group (RASI group) and then we compared the different incidences of NODM between the CCB with RASI and CCB group.

DM in addition to hypertension may amplify the progression of vascular damage. Coexistence of DM and hypertension also are important factors of arterial stiffness and endothelial dysfunction compared with hypertensive non-diabetic patients.[23] Several possible cause-effect relationships between DM and hypertension were hypothesized including obesity and insulin resistance, inappropriate activation of the renin-angiotensin-aldosterone system, oxidative stress, increased sympathetic nervous system activation, and abnormal renal handling of sodium.[24] Also hypertension causes endothelial dysfunction, remodeling of small arteries and/or sustained sympathetic nervous system acti-

vation; these factors can cause insulin resistance and diabetes by reducing insulin delivery to muscles or causing pancreatic microvascular dysfunction.[4]

Previous studies reported that CCB combined with ARB had metabolically neutral effects.[6] Our study also showed that the use of RASI in addition to CCB did not show a significant reduction of the development of NODM. Although several possible mechanisms that cause change in insulin sensitivity were suggested, the precise mechanisms are not clear currently.[7] Although we cannot precisely explain this result, we cautiously speculate several possible factors related to our results. Firstly, there may be similar or common pathways increasing insulin sensitivity between CCB and RASI and these pathways fail to show synergistic effects on insulin sensitivity of both drugs and may also leads to insignificant differences on the incidence of NODM. Secondly, as we know, there is some debate[15–17,22] about comparative superiority of beneficial effects between ACEI and ARB on the incidence of NODM in hypertensive patients, the countervailing effect may have nullified the beneficial effect between these two groups. Thirdly, there are so many different kinds and numbers of drugs that compose the RASI group and diverse drug interactions also can decrease their beneficial effects on insulin sensitivity by interacting with each other (Table 3). Last but not least, this study was a single center retrospective study, so this may be another factor of this result.

Owing to the incidence of NODM differed in the studies and because they were sometimes combined with other antihypertensive drugs and no monotherapy was considered, the accurate estimation of the annual incidence to the different substance classes may be difficult. In general, independent from the substance class, the incidence was estimated at 1.7% annually.[14] The incidence of NODM during treatment with CCB varies from 0.9% to 2.0% per year and from 1.1% to 1.7% per year by ACEI.[14] Ahmad, *et al*.[25] reported that the incidence of NODM was increased with the duration of antihypertensive drug therapy (three- and five-years) and the incidence of NODM was 12.5% by CCB during one- and five-years follow-up period. In our study, the incidence of NODM was similar with his study (8.6% *vs*. 6.8%, Table 2) during the four-year follow-up periods.

In our study, the higher rate of total death in RASI group before PSM may be caused by relatively higher baseline risk factors such as, SBP, DBP, previous PCI, current alcoholics, triglyceride, and the use of diuretics, statin, aspirin, and clopidogrel which were contained in this group.

Despite the above cited limitations, our study included real-world combination drug therapy in hypertensive Korean patients. We believe this study to be the first comparative study to investigate whether or not there are additional beneficial effects of RASI on the incidence of NODM over CCB monotherapy during four-year follow-up period in Korea.

4.1 Limitations

Our study has several limitations. Firstly, we have some deficits in several parameters such as family history, abdominal circumference, and socioeconomic status. Secondly, the study population of this study was relatively low-risk patients, so these results could be different in high-risk patients. Thirdly, though the first antihypertensive prescription for nearly all patients was monotherapy, the decision to add a second antihypertensive drug was dependent up on each physician's discretion; this could affect the end results and add a bias to this study. Fourthly, the RASI group was composed of so many diverse kinds and numbers of drugs and this factor also add bias. Last but not least, because this study was a single center retrospective study, large, randomized, and controlled clinical trials will be required for a more definitive conclusion.

4.2 Conclusions

In conclusion, the use of RASI in addition to CCB showed comparable incidence of NODM and MACE compared to CCB monotherapy in non-diabetic hypertensive Korean patients up to four years. However, large-scaled randomized controlled clinical trials will be required for a more definitive conclusion.

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