Real-world use of ACEI/ARB in diabetic hypertensive patients before the initial diagnosis of obstructive coronary artery disease: patient characteristics and long-term follow-up outcome

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Research

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Abstract

Background: Current guidelines recommend angiotensin-converting-enzyme inhibitors (ACEI) /angiotensin receptor blockers (ARB) as a first-line therapy in diabetic hypertensive patients and for secondary prevention in patients with obstructive coronary artery disease (OCAD). However, the effects of using ACEI/ARB before the initial diagnosis of OCAD on major adverse cardiac and cerebral event (MACCE) in diabetic hypertensive patients remain unclear. This study investigated whether using ACEI/ARB before the initial diagnosis of OCAD could be associated with improved clinical outcomes in diabetic hypertensive patients.

Methods: A total of 2501 patients with hypertension and diabetes, who were first diagnosed with OCAD by coronary angiography, were included in the analysis. Of the 2501 patients, 1300 did not used ACEI/ARB before the initial diagnosis of OCAD [the ACEI/ARB(-) group]; 1201 did [the ACEI/ARB(+) group]. Propensity score matching at 1:1 was performed to select 1050 patients from each group. Incidence of acute myocardial infarction (AMI), infarct size in patients with AMI, heart function, and subsequent MACCE during a median of 25.4-month follow-up were determined and compared between the 2 groups.

Results: Compared with the ACEI/ARB(-) group, the ACEI/ARB(+) group had significantly lower incidence of AMI (22.5% vs. 28.4%, p=0.002), smaller infarct size in patients with AMI (pTNI: 5.7 vs. 6.8 ng/ml, p=0.044; pCKMB: 21.7 vs. 28.7 ng/ml, p=0.028), better heart function (LVEF: 60.0 vs. 58.5%, p=0.002), and lower incidences of non-fatal stroke (2.4% vs. 4.6%, p=0.015) and composite MACCE (23.1% vs. 29.7%, p=0.026). No prior ACEI/ARB therapy was significantly and independently associated with non-fatal stroke and composite MACCE.

Conclusions: In diabetic hypertensive patients, treatment with ACEI/ARB before the initial diagnosis with OCAD was associated with decreased incidence of AMI, smaller infarct size, improved heart function, and lower incidences of non-fatal stroke and composite MACCE. Trial registration: retrospectively registered.

Background

Cardiovascular disease is the leading cause of death worldwide[1-3], especially obstructive coronary artery disease (OCAD). Hypertension and diabetes are strong independent risk factors for OCAD and associated with most of the cardiovascular death globally[4,5]. Individuals with both hypertension and diabetes are at a higher risk of OCAD than those with either of the two conditions[6].

It has been well known that the renin-angiotensin-aldosterone system (RAAS) plays an important role in regulating cardiovascular and renal function[7,8]. Randomized clinical trials have confirmed that suppression of RAAS activity by angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) can protect cardio-renal

function and reduce mortality[9-13]. Thus, the current guidelines recommend ACEI/ARB as a first-line therapy for diabetic hypertensive patients[14-16] and for secondary prevention in patients with OCAD[17,18].

It has been generally accepted that diabetic hypertensive patients can benefit from ACEI/ARB; however, previous studies have found the ACEI/ARB is underutilized in these patients[19-21]. The real-world use of ACEI/ARB in diabetic hypertensive patients in China remains unclear. Diabetic hypertensive patients are prone to develop OCAD. Most previous studies have emphasized the secondary preventive effects of ACEI/ARB on OCAD. Whether starting ACEI/ARB therapy before the initial diagnosis of OCAD could improve patient outcomes is still unknown. The current study aimed to fill this knowledge gap. We used the Cardiovascular Center Beijing Friendship Hospital Database Bank to evaluate the effectiveness of ACEI/ARB therapy on improving major adverse cardiac and cerebral event (MACCE) outcomes in diabetic hypertensive patients.

Methods

Study population

Patients' records in the Cardiovascular Center of Beijing Friendship Hospital Database Bank were screened. As shown in **Figure 1**, the records of 10,098 patients undergoing coronary angiography from December 2012 to February 2019 in our center were screened. Of them, 8385 patients were diagnosed with OCAD. Of the 8385 patients, 5884 were excluded according to the exclusion criteria, which were 1) with prior diagnosis of OCAD, 2) with severe valvulopathy or cardiomyopathy and without hypertension and/or diabetes, 3) with acute infections disease, rheumatic disease, hematological disease, or neoplastic disease, 4) lacking clinical or follow-up data, and 5) with eGFR<30ml/min/1.73m^2. Finally, 2501 patients were included in this analysis. Of the 2501 patients, 1300 were not treated with ACEI/ARB before the initial diagnosis of OCAD; 1201 were confirmed to receive ACEI/ARB treatment before the diagnosis. All patients were followed up to May 31, 2019 with a median follow up of 25.4 months (IQR: 12.3-48.6 months).

Data collections and definitions

The data collection process was approved by the Institutional Review Board of Beijing Friendship Hospital affiliated to Capital Medical University and was in accordance with the Declaration of Helsinki.

Patients' demographics, medical and medication history, laboratory test results, echocardiographic and angiographic evaluation results, and clinical outcomes during the hospitalization after the initial

diagnosis of OCAD were collected and verified using an electronic medical recording system. The outcomes from MACCE were collected and recorded during clinical follow-up visits.

OCAD was defined as atherosclerotic lesions in coronary arteries causing ≥50% of the lumen obstruction by coronary angiography, causing myocardial ischemia or necrosis. Hypertension refers to systolic blood pressure ≥140mmHg and/or diastolic blood

pressure ≥90mmHg measured in clinic at three different times on different days in a

quiet state or under the treatment with antihypertensive drugs. Diabetes was defined as receiving treatment with glucose-lowering medication, glycosylated hemoglobin ≥6.5%, fasting serum glucose ≥126 mg/dL, or non-fasting serum glucose ≥200 mg/dL.

MACCE included all-cause death, non-fatal MI, non-fatal stroke, revascularization, and cardiac rehospitalization (admission because of angina or heart failure). All-cause death was defined as the incidence of cardiovascular death or non-cardiovascular death. Cardiovascular death was defined as fatal stroke and myocardial infarction, sudden death, and other cardiovascular death. Any coronary revascularization was defined as a revascularization of the target vessel or non-target vessels. Non-fatal MI was defined as chest pain with new ST-segment changes and elevation of myocardial necrosis markers

to at least twice of the upper limit of the normal range. Non-fatal stroke, including

ischemic and hemorrhagic stroke, was defined as cerebral dysfunction caused by

cerebral vascular obstruction or sudden rupture and was diagnosed based on signs of neurological dysfunction or evidence of brain imaging. Cardiac rehospitalization refers to rehospitalization for angina pectoris or heart failure.

Statistical analyses

Continuous variables are presented as mean ± standard deviation (SD) or median (IQR).

Comparisons between the two study groups were analyzed by Student's t-test or Mann-Whitney U-test. Categorical variables are expressed as number and percentage and compared using the Pearson chi-square test or Fisher's exact test. To control confounding factors, we performed propensity score matching. The cumulative

incidence of MACCE was estimated by Kaplan-Meier survival curves. A multivariable Cox regression analysis was performed to identify independent predictors for composite MACCE. Baseline variables that were significantly correlated with outcomes by univariate analysis and clinically relevant were used in the multivariate model. For the COX regression, the outcome event is at least 15-20 times the number of variables. Thus, the included variables for the COX regression were carefully chosen, given the number of events available, to ensure parsimony of the final model. All

analyses were two-tailed and P value <0.05 was considered statistically significant.

Data were analyzed using the statistical analysis software IBM SPSS statistics 24.0.

Propensity score matching

Propensity score matching was used to reduce selection bias in this study. The matching process was conducted with a minimum-distance scoring method and a 1-to-1 match between the ACEI/ARB(-) group and the ACEI/ARB(+) group. In this study, propensity scores were calculated through a binary logistic regression model, including covariates of age, sex, body mass index (BMI), fasting blood glucose (FBG), hemoglobin (HGB), estimated glomerular filtration rate (eGFR), low-density lipoprotein cholesterol (LDL-C), history of smoking and dyslipidemia, previous medication history including antiplatelet agent, beta-blocker, and statins. Ultimately, 1050 ACEI/ARB(+) patients were individually 1:1 matched to 1050 ACEI/ARB(-) controls using nearest available score matching. The statistical analysis software SPSS version 24.0 was used for the matching.

Results

Patient characteristics

As shown in **Figure 1**, of the 2501 eligible patients, 1201 patients (48.0%) used ACEI/ARB before the hospital admission; 1300 (52.0%) did not. Comparing with the ACEI/ARB (+) group, the ACEI/ARB (-) group showed significantly higher percent of male, lower BMI, higher heart rate, lower percent of dyslipidemia, and significantly less likely to receive antiplatelet therapy, beta-blocker or statins before the hospital admission for OCAD. In-hospital medical and interventional treatments were similar between the 2 groups except that significantly fewer patients treated with ACEI/ARB in the ACEI/ARB (-) group than in the ACEI/ARB (+) group (52.1% vs. 83.9%, p<0.001) during hospitalization. Subjects in the ACEI/ARB (-) group had a significant longer average hospital stay (**Table 1**).

As presented in **Table 2**, the ACEI/ARB(-) group had significantly higher white cell count, neutrophil count and higher levels of sensitivity C reactive protein (hsCRP), HGB, FBG, random blood glucose(RBG) at admission, eGFR, and LDL-C than the ACEI/ARB(+) group. Echo evaluation showed that the ACEI/ARB(-)

group had significantly greater left ventricular end-systolic diameter (LVESD) and left ventricular end-systolic volume (LVESV) and lower left ventricular ejection fraction (LVEF), left ventricular fraction shortening (LVFS) and stroke volume (SV) than the ACEI/ARB(+) group. Angiographically, there was no significant difference between the 2 groups.

Correlation analysis of ACEI/ARB therapy and baseline variables revealed that patients with BMI ≥25kg/m^2, previous use of antiplatelet agent, beta-blocker and statins were more likely to receive ACEI/ARB therapy before the hospital admission. However, patients with AMI at admission and a previous history of using calcium channel blocker (CCB) were less likely to receive ACEI/ARB therapy before the hospital admission (**Figure 2**).

Propensity score matching

Propensity scores of 1050 ACEI/ARB users were 1:1 matched to 1050 patients without using ACEI/ARB before the initial diagnosis of OCAD. There were no significant differences in baseline clinical characteristics and medical history between the propensity score matched (PSM) ACEI/ARB(-) and ACEI/ARB(+) groups except that the PSM ACEI/ARB(-) group had significantly fewer patients treated with ACEI/ARB therapy during the hospitalization (51.0% vs. 83.9%, p<0.001, **Table 1**).

The ACEI/ARB(-) group had significantly higher hsCRP levels than the ACEI/ARB(+) group. Echo evaluation showed that the ACEI/ARB(-) group had significantly larger LVESD, lower LVEF and LVFS than the ACEI/ARB(+) group (**Table 2**).

The ACEI/ARB(-) group had a significantly higher incidence of AMI at the admission than the ACEI/ARB(+) group (28.4% vs. 22.5%, p=0.002, **Figure 3**). The peak levels of serum myoglobin (Myo), creatine kinase MB (CKMB), and cardiac troponin I (cTnI) were used to estimate infarct size. We found no difference in pMyo between the 2 groups. The peak levels of serum CKMB and cTnI were significantly higher in the ACEI/ARB(-) group (p-CKMB: 28.7 vs. 21.7ng/mL, p = 0.028; p-cTnI: 6.8 vs. 5.7ng/mL, p = 0.044, **Table 3**).

In-hospital clinical outcomes

The ACEI/ARB(-) group had significantly higher incidence of non-fatal stroke than the ACEI/ARB(+) group (Before propensity score matching: 1.6% vs. 0.7%, p=0.047; After propensity score matching:1.7% vs.

0.8%,p=0.048). There was no statistical difference in the other MACCE between the 2 groups.

Subsequent MACCE and mortality

During a median of 25.4 months (IQR: 12.3-48.6 months) follow-up, composite MACCE occurred in 28.7% of patients in the ACEI/ARB (-) group and 23.1% in the ACEI/ARB (+) group (HR=1.23, 95%CI: 1.06-1.44, p=0.008, Table 4). All-cause mortality was observed in 4.5% of the patients in the ACEI/ARB(-) group and 4.7% of the patients in the ACEI/ARB (+) group (HR=0.92, 95%CI: 0.64-1.32, p=0.644). Cardiovascular death occurred in 3.8% of the patients in the ACEI/ARB (-) group and 3.1% in the ACEI/ARB (+) group (HR=1.18, 95%CI: 0.77-1.81, p=0.439). Non-fatal stroke occurred in 4.0% of the patients in the ACEI/ARB (-) group and 2.4% in the ACEI/ARB (+) group (HR=1.62, 95%CI: 1.03-2.56, p=0.037). Subsequent non-fatal MI, revascularization, and cardiac rehospitalization were not statistically different between the 2 groups.

After propensity-score matching, composite MACCE occurred in 29.7% of the patients in the PSM ACEI/ARB(-) group and 23.1% in the PSM ACEI/ARB(+) group (HR=1.21, 95%CI: 1.02-1.43, p=0.026, **Table 4**); all-cause mortality was observed in 5.0% of the patients in the PSM ACEI/ARB(-) group and 4.9% in the PSM ACEI/ARB (+) group (HR=0.95, 95%CI: 0.65-1.40, p=0.811); Cardiovascular death was identified in 4.2% of PSM ACEI/ARB (-) group and 3.1% of the PSM ACEI/ARB (+) group (HR=1.24, 95%CI: 0.79-1.94, p=0.355); non-fatal stroke occurred in 4.6% of the PSM ACEI/ARB (-) group and 2.4% of the PSM ACEI/ARB (+) group (HR=1.82, 95%CI: 1.13-2.96, p=0.015). Subsequent non-fatal MI, revascularization, and cardiac rehospitalization were not statistically different between the 2 groups. The Kaplan-Meier curves show that the

ACEI/ARB(-) group had significantly higher cumulative rate of non-fatal stroke and composite MACCE than the ACEI/ARB (+) group (**Figure 4**). The cumulative rate of all cause death, cardiovascular death, non-fatal MI, revascularization, and cardiac rehospitalization were not statistically different between the 2 groups.

Independent association between non-fatal stroke and subsequent MACCE

In the multivariate analysis, we included variables that were identified to be significantly associated with non-fatal stroke and composite MACCE in the univariate model. The multivariate analysis revealed that no prior ACEI/ARB therapy, previous history of stroke, increased number of involved vessels, and lower LVEF were independently associated with non-fatal stroke (**Table 5**); no prior ACEI/ARB therapy, previous history of stroke, increased number of involved vessels, lower eGFR, lower LVEF, and no-antiplatelet therapy in hospital were significantly and independently associated with subsequent composite MACCE (**Table 6**).

Discussion

To the best of our knowledge, the current study was the first to investigate whether ACEI/ARB used before the initial diagnosis of OCAD in diabetic hypertensive patients could be associated with improved clinical outcomes. We found that use of ACEI/ARB before the initial diagnosis of OCAD was associated with reduced incidence of AMI, reduced myocardial infarction size, and improved cardiac function, whereas we found no significant correlation between the prior ACEI/ARB therapy and mortality. However, the incidences of non-fatal stroke and composite MACCE were significantly higher in the ACEI/ARB(-) group than in the ACEI/ARB(+) group. No prior ACEI/ARB therapy was an independent predictor of non-fatal stroke and composite MACCE.

ACEI promotes vasodilation by inhibiting angiotensin II formation and bradykinin decomposition, and ARB can trigger vasodilation and natriuresis. Therefore, ACEI/ARB are considered as antihypertensive drugs. In addition to the antihypertensive effects, ACEI/ARB has other pleiotropic clinical beneficial effects, such as inhibiting ventricular remodeling, decreasing sympathetic activity, improving insulin resistance, inhibiting atherosclerosis process, inhibiting thrombosis and platelet aggregation, and improving endothelium function and plaque stabilization[22-25]. Previous studies[11,12,26] have supported that ACEI/ARB exert clinical beneficial effects beyond blood pressure reduction and can reduce the incidence of major adverse cardiac events.

The current guidelines recommend ACEI/ARB as a first-line drug for diabetic hypertensive patients[14-16]; however, the reported effects of ACEI/ARB on cardiovascular risk in these patients are controversial. Previous studies have found that patients treated with ACEI/ARB showed lower incidences of AMI[27-29] and stroke[28,30,31] than the control group. In addition, the Captopril Prevention Project (CAPPP)[29] has shown that compared with the diuretic/beta-blocker therapy group, the captopril group had lower incidences of cardiovascular mortality and all-cause mortality. A meta-analysis has demonstrated that ACEI/ARB was associated with a 17% reduction in cardiovascular mortality in diabetic hypertensive patients; however, ACEI/ARB was not associated with MI, stroke and all-cause mortality[32]. On the contrary, Bosch et al[33] have shown that ACEI was not beneficial in the prevention of stroke. In addition, the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, which recruited 2018 patients with T_2DM, failed to find a reduction in cardiovascular morbidity in patients using ARB[34]. A recent meta-analysis[12] has shown that ACEI significantly reduced the risk of AMI, cardiovascular mortality, and all-cause mortality, whereas treatment with ARBs did not show these benefits. In addition, neither ACEI nor ARB therapy decreased the incidence of stroke in patients with diabetes. Strauss et al[35] believed that ARB could not reduce the risk of AMI, cardiovascular mortality, or all-cause Mortality. In the

current study, we found that compared with diabetic hypertensive patients who did not use ACEI/ARB before the initial diagnosis of OCAD, those who did had significantly lower incidence of OCAD-associated AMI at the hospital admission and lower incidences of non-fatal stroke and composite MACCE during follow-up. Multivariate analyses revealed that no prior ACEI/ARB therapy was an independent predictor of non-fatal stroke and composite MACCE. These findings have not been reported previously. There were 249 patients (23.7%) using ACEI and 801 patients (76.3%) using ARB before the initial diagnosis of OCAD in the PSM ACEI/ARB(+) group in this study. The incidence of AMI in the ACEI users and ARB users was 24.1% (60/249) and 22.0% (176/801), respectively, and the incidence of AMI in the PSM ACEI/ARB(-) group was 28.4% (298/1050). Therefore, we believed that both ACEI and ARB can reduce AMI development.

Notably, we found that the ACEI/ARB(-) group had significantly higher levels of hs-CRP, pTNI, and pCK-MB and lower LVEF than the ACEI/ARB(+) group, indicating that the patients who did not use ACEI/ARB before the initial diagnosis of OCAD appeared to have higher levels of inflammation, larger myocardial infarction area, and poorer cardiac function. Consistently, Gong et al[36] also found that previous treatment with ACEI/ARB/β-blocker was associated with better heart function and smaller infarct size. To the best of our knowledge, this is the first study focusing on the effect of ACEI/ARB on the severity of the AMI in diabetic hypertensive patients.

The current study found that 52.0% (1300/2501) of patients with diabetic hypertension and diagnosed with OCAD for the first time did not use ACEI/ARB therapy. Notably, the proportion of patients treated with ACEI/ARB during hospitalization and long-term follow up in the ACEI/ARB(-) group was 51.0% and 41.3%, respectively, which were substantially lower than the proportions in the ACEI/ARB(+) group (83.9% and 67.0%, respectively). A study from the United States (from six states, 57,1483 participants) has shown that about 52.5% of patients with diabetic hypertension were non-adherent to ACEI/ARB therapy, which was related to an increased risk for diabetes-related rehospitalizations[19]. All these findings suggest that the real-world use of ACEI/ARB is seriously insufficient worldwide and the underutilization of ACEI/ARB may lead to poor clinical outcomes. We analyzed the factors associated with the use of ACEI/ARB and found that patients who have previously used CCB were less likely to receive ACEI/ARB therapy before the hospital admission, suggesting that CCB might affect ACEI/ARB' first-line status in diabetic hypertensive patients. Based on the recommendations of the current guidelines[14-16], we believe the first-line treatment status of ACEI/ARB in patients with diabetic hypertension still need to be emphasized.

Limitations

First, this is a single-center study although including a large sample size; thus, generalization of the findings should be cautious. Second, this is a retrospective observational study. The information on the dosage of ACEI/ARB was limited. Prospective cohort studies are required to confirm our findings.

Conclusions

Use of ACEI/ARB therapy for diabetic hypertensive patients before the initial diagnosis of OCAD was significantly associated with lower incidence of AMI, improved heart function, smaller infarct size, and lower incidences of non-fatal stroke and composite MACCE. No prior ACEI/ARB therapy was significantly and independently associated with non-fatal stroke and composite MACCE. ACEI/ARB therapy was largely underutilized in diabetic hypertensive patients.

Abbreviations

ACEI/ARB: Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers; OCAD: Obstructive coronary artery disease; MACCE: Major adverse cardiac and cerebral event; AMI: Acute myocardial infarction; Myo: Myoglobin; CKMB: Creatine kinase MB; cTnI: Cardiac troponin I; RAAS: Renin-angiotensin-aldosterone system; BMI: Body mass index; FBG: Fasting blood glucose; RBG :Random blood glucose; HGB: Hemoglobin; eGFR: Estimated glomerular filtration rate; LDL-C: Low-density lipoprotein cholesterol; hsCRP: High sensitivity C reactive protein; LVESD: Left ventricular end-systolic diameter; LVESV: Left ventricular end-systolic volume; LVEF: Left ventricular ejection fraction; LVFS: Left ventricular fraction shortening; SV: Stroke volume; CCB: Calcium channel blocker; T_2DM: Type 2 diabetes mellitus.

Declarations

Funding

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study data collections were approved by the Institutional Review Board of Beijing Friendship Hospital affiliated to Capital Medical University, and written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from

the corresponding author on reasonable request.

Authors' contributions

YZ performed study, statistical analysis and wrote manuscript. XSD, BH and QBL participated in study data collection. HC contributed discussion and edited manuscript. XQZ designed study and revised manuscript. WPL designed study, performed statistical analysis and edited manuscript. HWL provided funding support, designed study and reviewed manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline clinical characteristics.

Characteristics	Before PS match			After PS match		
	ACEI/ARB(-)	ACEI/ARB(+)	p value	ACEI/ARB(-)	ACEI/ARB(+)	p value
	(n: 1300)	(n: 1201)		(n: 1050)	(n: 1050)	
Age, years	64.7±10.5	65.2±10.0	0.300	65.8±11.5	65.4±12.2	0.128
Male	774(59.5)	662(55.1)	0.026	578(55.0)	592(56.4)	0.539
BMI, kg/m^2	26.2±3.5	26.6±3.5	<0.001	25.9±3.4	26.2±3.5	0.319
SBP, mmHg	136.0±19.7	135.0±18.9	0.085	134.9±22.4	134.3±21.1	0.163
DBP, mmHg	76.9±12.3	75.7±11.5	0.179	74.8±12.3	74.5±13.3	0.108
Heart rate, bpm	74.1±13.0	71.9±12.1	<0.001	74.7±13.2	74.7±12.8	0.069
Medical history						
Current/ex-Smoker	628(48.3)	535(44.5)	0.060	473(45.0)	479(45.6)	0.793
CKD	34(2.6)	43(3.6)	0.163	29(2.8)	36(3.4)	0.378
Stroke	239(18.4)	243(20.2)	0.242	203(19.3)	207(19.7)	0.826
Dyslipidemia	580(44.6)	603(50.2)	0.005	478(45.5)	492(46.9)	0.540
Medication used before admission						
Antiplatelet agent	336(25.8)	428(35.6)	<0.001	312(29.7)	332(31.6)	0.344
Beta-blocker	283(21.8)	356(30.6)	<0.001	265(25.2)	280(26.7)	0.455
CCB	703(54.1)	617(51.4)	0.176	583(55.5)	543(51.7)	0.080
Diuretics	42(3.2)	51(4.2)	0.149	34(3.2)	45(4.3)	0.207
Statins	319(24.5)	457(38.1)	<0.001	315(30.0)	330(31.4)	0.478
In-hospital treatment						
PCI/CABG	918(70.6)	818(68.1)	0.174	719(68.5)	723(68.9)	0.851
Antiplatelet agent	1249(96.1)	1152(95.9)	0.841	1007(95.9)	1005(95.7)	0.828
ACEI/ARB	677(52.1)	1008(83.9)	<0.001	535(51.0)	881(83.9)	<0.001
Beta-blocker	940(72.3)	849(70.7)	0.371	760(72.4)	742(70.7)	0.384
CCB	586(45.1)	574(47.8)	0.173	485(46.2)	502(47.8)	0.457
Diuretics	94(7.1)	81(6.7)	0.634	79(7.5)	75(7.1)	0.269
Statins	1151(88.5)	1075(89.5)	0.438	935(89.0)	937(89.2)	0.888
Hospital stay, day	6(5,8)	6(4,8)	0.004	6(4,8)	6(4,8)	0.106

Data are presented as mean±SD , IQR or n (%).

ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CKD: Chronic kidney disease; CCB: Calcium channel blocker; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft.

Table 2. Laboratory test results and echocardiographic and angiographic characteristics.

	Before PS match			After PS match		
	ACEI/ARB(-)	ACEI/ARB(+)	P value	ACEI/ARB(-)	ACEI/ARB(+)	P value
	(n: 1300)	(n: 1201)		(n: 1050)	(n: 1050)	
Laboratory values						
WBC, X10^9/L	6.8(5.6,8.7)	6.6(5.5,8.1)	0.024	8.4(6.3,10.1)	7.9(6.1,10.2)	0.477
Neutrophil, X10^9/L	4.5(3.6,5.9)	4.4(3.5,5.5)	0.036	5.9(4.3,7.7)	5.5(4.0,7.7)	0.417
Monocyte, X10^9/L	0.29(0.16,0.44)	0.27(0.16,0.41)	0.081	0.27(0.15,0.42)	0.28(0.16,0.41)	0.465
Hemoglobin, g/L	134.5±16.5	133.7±15.7	0.043	133.0±18.9	132.9±19.1	0.341
Hs-CRP, mg/L	2.7(1.0,10.4)	2.0(0.8,5.4)	<0.001	10.5(2.9,23.3)	6.1(2.0,16.7)	0.002
FBG, mmol/L	7.0(5.8,9.0)	6.8(5.7,8.3)	0.001	7.5(6.2,9.3)	7.5(6.3,10.2)	0.429
RBG at admission, mmol/L	9.9(7.5,13.3)	9.7(7.2,12.8)	0.045	10.8(8.1,14.6)	11.0(8.7,14.2)	0.635
Glycated hemoglobin,%	7.5±1.5	7.5±1.6	0.505	7.7±1.7	7.8±1.7	0.101
ALT,U/L	19.0(13.0,28.0)	18.0(13.0,27.0)	0.239	22.0(15.0,39.0)	21.0(14.0,35.0)	0.836
Creatinine, umol/L	76.0(65.3,88.1)	77.8(66.2,90.6)	0.049	81.8(70.6,96.9)	81.0(68.7,94.0)	0.632
eGFR, ml/min/1.73m²	84.9(71.4,97.9)	82.3(67.9,95.3)	<0.001	79.1(64.5,94.5)	79.2(64.0,95.2)	0.797
TC, mmol/L	4.3(3.6,5.0)	4.2(3.4,4.9)	0.253	4.45±0.97	4.48±1.12	0.488
TG, mmol/L	1.5(1.1,2.2)	1.5(1.1,2.1)	0.874	1.5(1.1,2.0)	1.7(1.2,2.3)	0.080
LDL-C, mmol/L	2.4(1.9,2.9)	2.3(1.8,2.8)	<0.001	2.6(2.1,3.1)	2.6(2.0,3.1)	0.366
HDL-C, mmol/L	1.0(0.9,1.2)	1.0(0.9,1.2)	0.244	1.0(0.9,1.2)	1.0(0.8,1.2)	0.079
NT-Pro BNP,pg/ml	1621(644,4214)	1585(521,4548)	0.932	1855(657,4571)	1585(487,4357)	0.524
Echocardiographic values						
LVEDD, cm	5.06±0.49	5.04±0.48	0.574	5.13±0.51	5.17±0.52	0.892
LVESD, cm	3.28±0.57	3.21±0.51	0.001	3.53±0.59	3.51±0.61	0.037
LVEF, %	63.93±8.92	65.66±7.51	<0.001	58.46±9.40	59.97±9.66	0.002
LVFS, %	35.33±6.22	36.52±5.92	<0.001	31.4±6.18	32.80±7.23	0.001
LVEDV, ml	122.9±28.3	122.2±27.9	0.574	127.5±30.0	129.9±31.9	0.979
LVESV, ml	41.0(32.2,51.2)	38.2(32.2,48.4)	0.002	47.4(38.8,65.9)	47.4(36.7,62.0)	0.063
LA,cm	3.71±0.43	3.74±0.41	0.038	3.76±0.45	3.78±0.42	0.199
E/A	0.80(0.68,1.00)	0.79(0.68,1.00)	0.093	0.84(0.69,1.16)	0.81(0.67,1.16)	0.110
SV,ml	76.7(66.5,87.9)	79.2(68.7,88.9)	0.017	70.8(63.4,83.7)	75.4(65.4,87.1)	0.075
Angiography values						
Involved vessel						
Single vessel	180(13.8)	158(13.2)	0.614	157(15.0)	138(13.1)	0.233
Multi-vessel/LM	1120(86.2)	1043(86.8)		893(85.0)	912(86.9)	
CTO	122(9.4)	108(9.0)	0.735	92(8.8)	88(8.4)	0.755
Proximal LAD	697(53.6)	626(52.1)	0.455	557(53.0)	551(52.5)	0.793

Data are presented as mean±SD , IQR or n(%)

WBC: white blood cell count; Hs-CRP: High sensitivity C reactive protein; FBG: Fasting blood glucose; RBG :Random blood glucose; ALT: Alanine transaminase; eGFR: estimated Glomerular filtration rate; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; NT-Pro BNP: N-terminal pro-brain natriuretic peptide; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LVEF: Left ventricular ejection fraction; LVFS: Left ventricular fraction shortening; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LA: left atrium; E/A: ratio of early to late ventricular filling velocities; SV: Stroke volume; LM: Left main coronary artery; CTO: Chronic total occlusions; LAD: Left anterior descending.

Table 3. The estimated infarction size in patients with AMI.

The peak value of myocardial enzyme	Before PS match		P value	After PS match		P value
	ACEI/ARB(-)	ACEI/ARB(+)		ACEI/ARB(-)	ACEI/ARB(+)	
	(n: 402)	(n: 251)		(n: 298)	(n: 236)	
pMYO,ng/ml	50.1(26.0,150.3)	46.0(17.4,146.5)	0.090	50.4(28.3,173.8)	46.1(17.8,150.0)	0.063
pCK-MB,ng/ml	28.4(8.0,116.0)	21.3(5.2,89.2)	0.019	28.7(8.2,119.3)	21.7(5.2,90.9)	0.028
pTNI,ng/ml	7.7(2.3,27.0)	5.4(1.0,22.5)	0.003	6.8(2.2,22.9)	5.7(1.0,24.3)	0.044

Data are presented as IQR

AMI: Acute myocardial infarction; ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; pMYO: The peak value of myoglobin; pCK-MB: The peak value of Creatine kinase MB; pTNI: The peak value of troponin I.

Table 4. Clinical events during long-term follow-up.

	ACEI/ARB(-)	ACEI/ARB(+)	HR(95%CI)	p value
Overall population				
Number	1300	1201		
Composite MACCE	373(28.7)	277(23.1)	1.23(1.06,1.44)	0.008
All cause death	59(4.5)	57(4.7)	0.92(0.64,1.32)	0.644
CV death	49(3.8)	37(3.1)	1.18(0.77,1.81)	0.439
Non-fatal MI	57(4.4)	37(3.1)	1.38(0.91,2.08)	0.130
Non-fatal stroke	52(4.0)	29(2.4)	1.62(1.03,2.56)	0.037
Revascularization	102(7.8)	92(7.7)	0.98(0.74,1.29)	0.865
Cardiac rehospitalization	290(22.3)	233(19.4)	1.12(0.94,1.33)	0.208
Matched population				
Number	1050	1050		
Composite MACCE	312(29.7)	242(23.1)	1.21(1.02,1.43)	0.026
All cause death	53(5.0)	51(4.9)	0.95(0.65,1.40)	0.811
CV death	44(4.2)	33(3.1)	1.24(0.79,1.94)	0.355
Non-fatal MI	48(4.6)	31(3.0)	1.45(0.92,2.28)	0.106
Non-fatal stroke	48(4.6)	25(2.4)	1.82(1.13,2.96)	0.015
Revascularization	76(7.2)	81(7.7)	0.85(0.62,1.16)	0.300
Cardiac rehospitalization	241(23.0)	202(19.2)	1.09(0.91,1.32)	0.356

ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; MACCE: Major adverse cardiac and cerebral event; CV: Cardiovascular; MI: Myocardial infarction; HR: Hazard ratio; CI: Confidence interval.

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All cause death	59(4.5)	57(4.7)	0.92(0.64,1.32)	0.644
CV death	49(3.8)	37(3.1)	1.18(0.77,1.81)	0.439
Non-fatal MI	57(4.4)	37(3.1)	1.38(0.91,2.08)	0.130
Non-fatal stroke	52(4.0)	29(2.4)	1.62(1.03,2.56)	0.037
Revascularization	102(7.8)	92(7.7)	0.98(0.74,1.29)	0.865
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All cause death	53(5.0)	51(4.9)	0.95(0.65,1.40)	0.811
CV death	44(4.2)	33(3.1)	1.24(0.79,1.94)	0.355
Non-fatal MI	48(4.6)	31(3.0)	1.45(0.92,2.28)	0.106
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ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; MACCE:
Major adverse cardiac and cerebral event; CV: Cardiovascular; MI: Myocardial infarction;
HR: Hazard ratio; CI: Confidence interval.

Table 5. Multivariate COX regression analysis of non-fatal stroke.

|	Univariate		Multivariate	
	HR(95%CI)	P value	Adjusted HR(95%CI)	P value
Age, y	1.02(0.99,1.05)	0.093	0.99(0.97,1.02)	0.661
ACEI/ARB(-)	1.82(1.13, 2.96)	0.015	1.72(1.05,2.84)	0.032
Beta-blocker before admission	0.54(0.29,1.01)	0.051	0.56(0.30,1.06)	0.074
Previous stroke	4.00(2.52,6.35)	<0.001	3.70(2.29,5.96)	<0.001
Hemoglobin, g/L	0.98(0.96,0.99)	0.003	0.99(0.97,1.01)	0.087
AMI at admission	2.10(1.32,3.35)	0.002	1.07(0.61,1.86)	0.813
LVEF,%	0.95(0.93,0.97)	<0.001	0.96(0.94,0.99)	0.003
Involved vessel	1.79(1.28,2.49)	0.001	1.52(1.08,2.14)	0.017
In-hospital treatment				
ACEI/ARB	0.72(0.46,1.14)	0.165	0.85(0.52,1.38)	0.504
Antiplatelet agents	0.34(0.16,0.75)	0.007	0.49(0.19,1.25)	0.136
Statins	0.43(0.24,0.76)	0.004	0.58(0.30,1.11)	0.101

ACEI/ARB(-): no Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker therapy
before admission; AMI: Acute myocardial infarction; LVEF: Left ventricular ejection fraction.

Table 6. Multivariate COX regression analysis of composite MACCE.

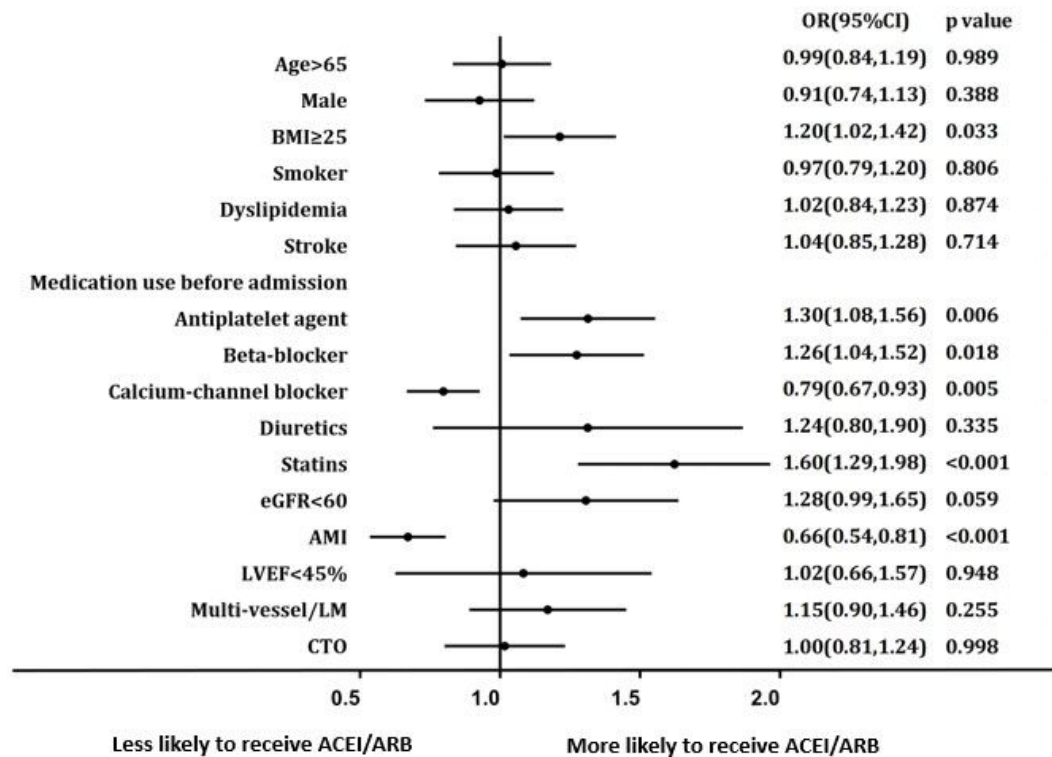|	Univariate		Multivariate	
	HR(95%CI)	P value	Adjusted HR(95%CI)	P value
Age,y	1.01(0.99,1.02)	0.081	1.00(0.99,1.01)	0.534
Male,%	1.05(0.89,1.25)	0.549	1.05(0.82,1.33)	0.715
ACEI/ARB(-)	1.21(1.02,1.43)	0.026	1.24(1.04,1.48)	0.019
Previous stroke	1.57(1.29,1.90)	<0.001	1.49(1.22,1.82)	<0.001
Smoking	1.09(0.93,1.29)	0.295	1.05(0.85,1.31)	0.646
Hemoglobin, g/L	1.00(0.99,1.00)	0.098	0.99(0.98,1.00)	0.496
Glycated hemoglobin,%	1.08(1.02,1.14)	0.007	1.05(0.99,1.11)	0.083
LDL-C, mmol/L	1.15(1.03,1.28)	0.015	1.07(0.95,1.20)	0.261
eGFR ml/min/1.73m^2	0.98(0.97,0.99)	<0.001	0.98(0.97,0.99)	0.044
AMI at admission	1.62(1.36,1.93)	<0.001	1.18(0.96,1.45)	0.119
LVEF,%	0.97(0.96,0.98)	<0.001	0.98(0.97,0.99)	<0.001
Involved vessel	1.45(1.29,1.62)	<0.001	1.34(1.19,1.51)	<0.001
CTO	1.49(1.23,1.81)	<0.001	1.07(0.87,1.33)	0.512
In-hospital treatment				
Antiplatelet agents	0.45(0.33,0.63)	<0.001	0.45(0.31,0.65)	<0.001
ACEI/ARB	0.92(0.78,1.09)	0.316	1.00(0.84,1.19)	0.973
Beta-blocker	0.93(0.78,1.12)	0.442	0.87(0.72,1.06)	0.164
Statins	0.75(0.58,0.95)	0.019	0.94(0.72,1.23)	0.653

ACEI/ARB(-): no Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker therapy before admission; LDL-C: Low-density lipoprotein cholesterol; eGFR: estimated Glomerular filtration rate; AMI: Acute myocardial infarction; LVEF: Left ventricular ejection fraction; CTO: Chronic total occlusions.
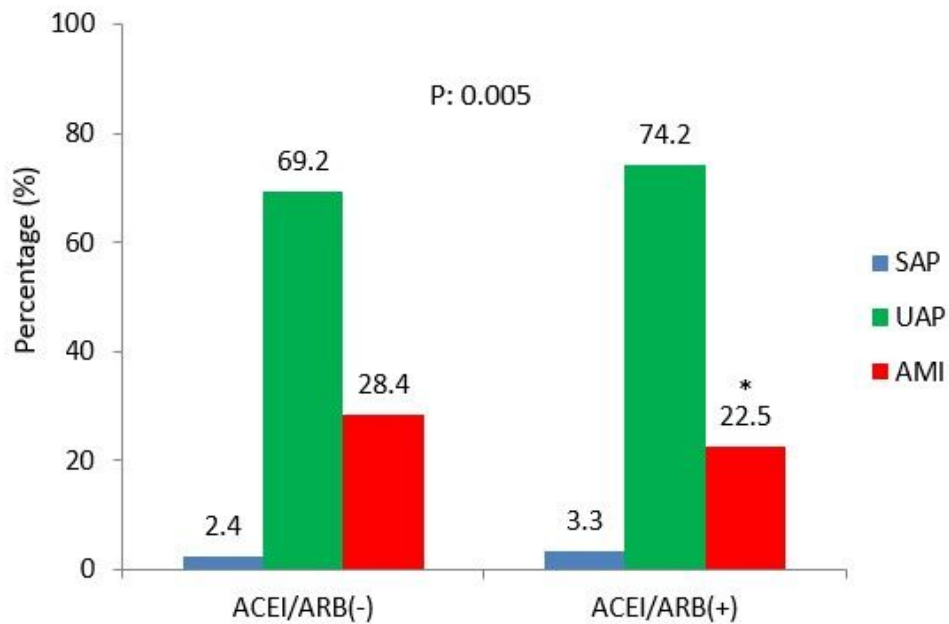
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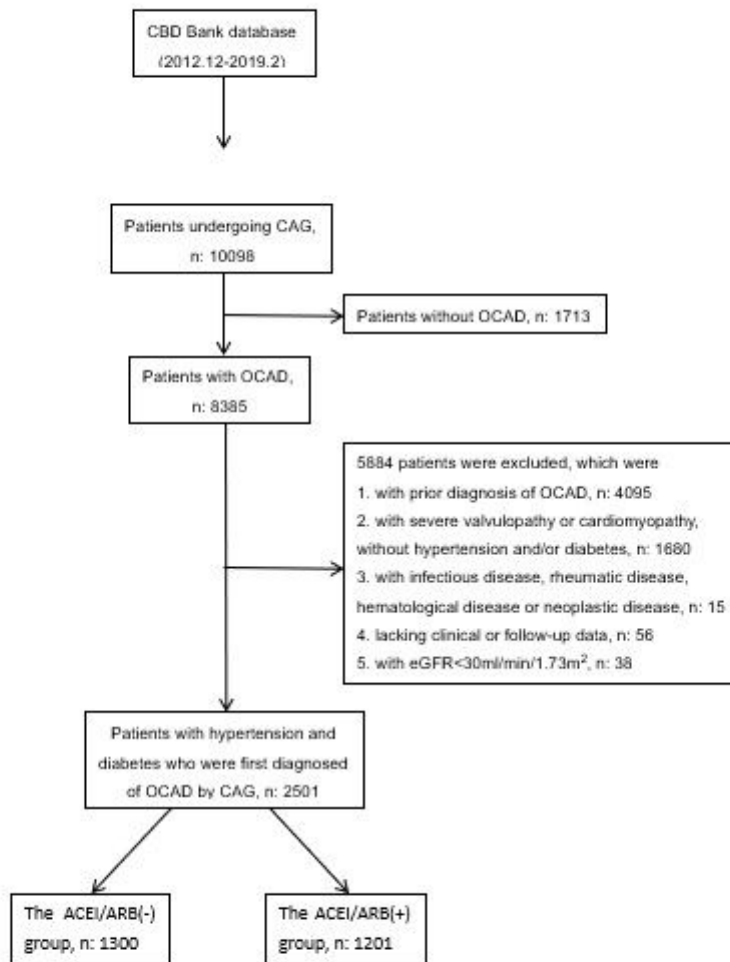
Figure 1

Patient flow chart. CBD: Cardiovascular Center of Beijing Friendship Hospital Database; CAG: Coronary angiography; OCAD: Obstructive coronary atherosclerotic disease; eGFR: estimated Glomerular filtration rate; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

	OR(95%CI)	p value
Age>65	0.99(0.84,1.19)	0.989
Male	0.91(0.74,1.13)	0.388
BMI≥25	1.20(1.02,1.42)	0.033
Smoker	0.97(0.79,1.20)	0.806
Dyslipidemia	1.02(0.84,1.23)	0.874
Stroke	1.04(0.85,1.28)	0.714
Medication use before admission		
Antiplatelet agent	1.30(1.08,1.56)	0.006
Beta-blocker	1.26(1.04,1.52)	0.018
Calcium-channel blocker	0.79(0.67,0.93)	0.005
Diuretics	1.24(0.80,1.90)	0.335
Statins	1.60(1.29,1.98)	<0.001
eGFR<60	1.28(0.99,1.65)	0.059
AMI	0.66(0.54,0.81)	<0.001
LVEF<45%	1.02(0.66,1.57)	0.948
Multi-vessel/LM	1.15(0.90,1.46)	0.255
CTO	1.00(0.81,1.24)	0.998

0.5 1.0 1.5 2.0

Less likely to receive ACEI/ARB   More likely to receive ACEI/ARB

Figure 2

Factors associated with ACEI/ARB use in multivariable analysis. Variables associated with ACEI/ARB use are shown along the vertical axis. The strength of effect is shown along the horizontal axis with the vertical line demarcating an odds ratio (OR) of 1 (i.e., no association); estimates to the right (i.e., > 1) are associated with a greater likelihood of ACEI/ARB use, whereas those to the left (i.e., < 1) indicate a reduced likelihood of ACEI/ARB use. Each dot represents the point estimate of the effect of that variable in the model, whereas the line shows the 95% confidence interval (CI). BMI: Body mass index; eGFR: estimated Glomerular filtration rate; AMI: Acute myocardial infarction; LVEF: Left ventricular ejection fraction; LM: Left main coronary artery; CTO: Chronic total occlusions.

Figure 3

Percentages of patients with SAP, UAP and AMI in 2 groups. SAP: Stable angina pectoris; UAP: Unstable angina pectoris; AMI: Acute myocardial infarction; ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker. *P: 0.002 versus ACEI/ARB(-) group.
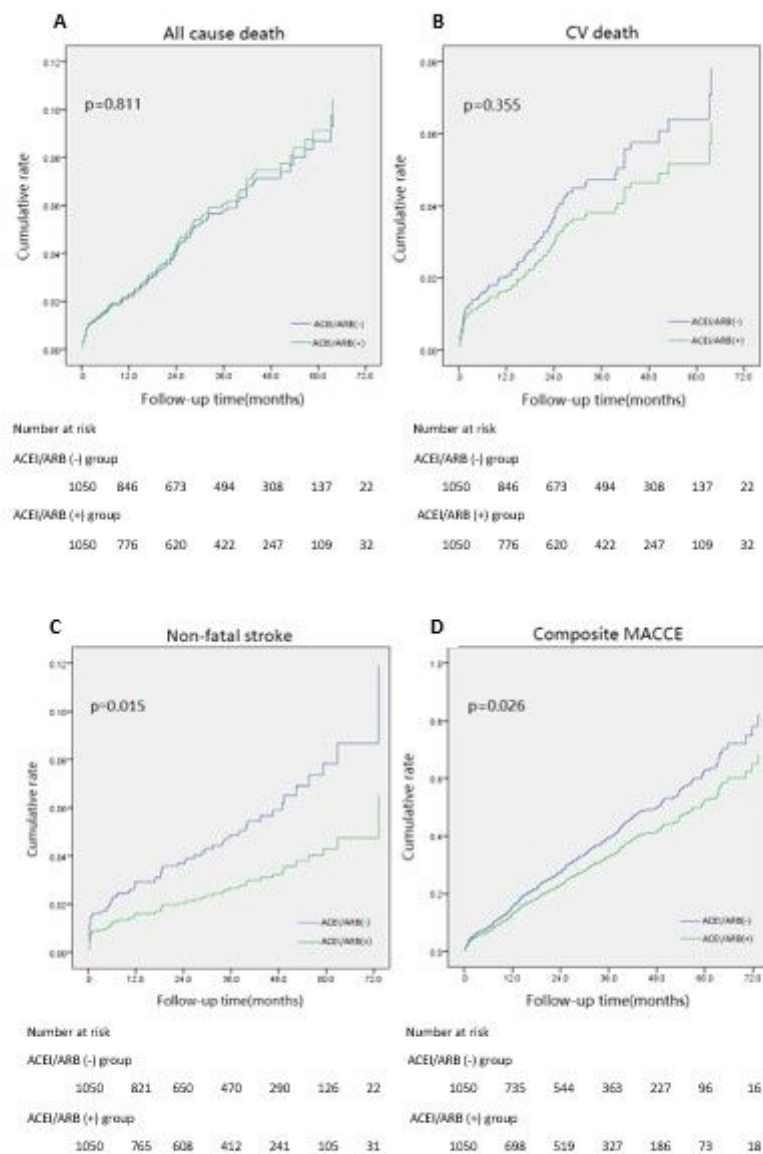
Figure 4

. Kaplan-Meier curve for all cause death(A)、CV death(B)、non-fatal stroke(C) and composite MACCE(D) of the ACEI/ARB(-) group (blue line) versus the ACEI/ARB(+) group (green line). ACEI/ARB: Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; CV: Cardiovascular; MACCE: Major adverse cardiac and cerebral event.