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Effects of a Secondary Prevention Combination Therapy with beta-Blocker and Statin on Major Adverse Cardiovascular Events in Acute Coronary Syndrome Patients

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Background: The efficacy of a beta-blocker or statin alone versus combination therapy is uncertain. We compared the effects of a combination of beta-blocker and statin with those of one-drug therapies with regard to the occurrence of a major adverse cardiovascular event (MACE) in patients with acute coronary syndrome (ACS).

Material/Methods: From 2011 to 2013, 636 ACS patients were included. Based on their risk category, enrolled subjects were assigned into 4 groups receiving consistent beta-blocker and/or statin treatment: no therapy group (n=139), with never use or inconsistent use beta-blocker and statin; beta-blocker monotherapy group (n=71); statin monotherapy group (n=149); and cotherapy group (n=277).

Results: Men composed 66.8% of the cohort, which had a mean age of 60.42±9.83 years. Compared with the no therapy group, the statin monotherapy group and cotherapy group had a lower risk of MACE (statin monotherapy group: adjusted hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.20-0.60, *P*<.001; cotherapy group: adjusted HR 0.16, 95% CI 0.09–0.28, *P*<.001). Subgroup analysis indicated that, compared with beta-blocker monotherapy and statin monotherapy, cotherapy significantly reduced the risks of MACE occurrences in ACS patients (beta-blocker monotherapy group: adjusted HR 0.28, 95% CI 0.13–0.59, *P*=.001; statin monotherapy group: adjusted HR 0.54, 95% CI 0.29–0.98, *P*=.044).

Conclusions: Beta-blocker and statin combination therapy lowered the risk of developing MACE in ACS patients.

MeSH Keywords: Acute Coronary Syndrome • Adrenergic beta-Antagonists • Hydroxymethylglutaryl-CoA Reductase Inhibitors

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Background

The therapeutic effects of beta-blockers and statins have been well demonstrated in reducing major adverse cardiovascular events (MACEs) [1–9]. However, the efficacy of a beta-blocker or statin alone versus combination therapy is less well established. Although a few previous studies showed that combined therapy with statin and beta-blocker was correlated with reduced short-term (30 days to 1 year) MACE occurrence in patients with coronary arterial disease [10–13], the long-term effects were still not clear. Therefore, we conducted a cohort study to investigate the long-term effects of the monotherapies and the combined therapy in patients with acute coronary syndrome (ACS). Results from this investigation provide novel evidence supporting the use of combination therapy with beta-blocker and statin in the clinical treatment of ACS.

Material and Methods

Study Population

A retrospective and observational cohort methodology was used in this study. During January 2011 to December 2013, 729 ACS subjects treated in Shaanxi Provincial People's Hospital were enrolled. Patients with incomplete data (21 patients), New York Heart Association (NYHA) cardiac functional class III or IV (10 patients), active infections (7 patient), immune system disease (6 patients), kidney disease (4 patients), and malignant tumor (2 patients) were excluded. Forty-three patients (6.3%) were excluded because they were lost to follow-up. Finally, 636 subjects were eventually included (Supplementary Figure 1).

Subjects were divided into 4 groups for beta-blocker and statin treatment based on their risk category: (1) no therapy group, which included never use and inconsistent use beta-blocker and statin; (2) beta-blocker monotherapy group, which was defined by consistent use of a beta-blocker and never use or inconsistent use of a statin; (3) statin monotherapy group, which was defined by consistent use of a statin and never use or inconsistent use of a beta-blocker; and (4) cotherapy group, which was defined by consistent and regular use of both a beta-blocker and a statin. For consistent use of a beta-blocker, patients were discharged with a beta-blocker and reported use in each interval. For never use of beta-blockers, patients were discharged without a beta-blocker and reported no use during the study interval. Inconsistent use of a beta-blocker meant that patients did not meet the criteria for either of the previous 2 patterns. For consistent use of a statin, patients were discharged with statin and reported use in each interval. For never use of a statin, patients were discharged without statin and reported no use during the study interval. Inconsistent use of a statin meant that patients did not meet the criteria for either of the previous 2 patterns.

Clinical data collection

Collected medical data were entered and maintained in the network database (Likang Times Technology Co. Ltd, Beijing, China). Raw data checking was performed by using the double entry method. Data eventually entered the database when the values of the 2 entries were consistent. Otherwise, the error would be automatically tagged by the system and corrected by checking the raw data.

Definitions

ACS was defined as high-risk unstable angina, non-ST-elevated myocardial infarction (MI), or ST-elevated MI, which were diagnosed by significant increases in serum creatine phosphokinase MB and troponin I. MACE endpoints included cardiovascular death, MI, ischemia-driven revascularization, progress to NYHA III or IV, and stroke. The definition of ischemia-driven revascularization was repeat percutaneous coronary intervention or coronary artery bypass grafting [14]. NYHA cardiac functional class III was defined as patients exhibiting obvious physical activity limitation due to cardiac diseases. Such patients are comfortable at rest, but even limited activity causes fatigue, palpitation, or dyspnea. NYHA functional class IV was defined as patients exhibiting an inability to carry on any physical activity without discomfort due to cardiac diseases. Symptoms are present even at rest or with minimal exertion. If any physical activity is undertaken, discomfort is increased [15].

Statistics

The baseline characteristics among the 4 groups were analyzed by analysis of variance (ANOVA) for parametric variables, the Kruskal-Wallis test for nonparametric variables, and the chi-square test for categorical variables. Cumulative event curves of MACEs were derived from the Kaplan-Meier method and the log-rank test was used for comparison. The impact of combination therapy with beta-blocker and statin on MACEs was estimated with univariate and multivariate Cox proportional hazards regression models. Four regression models were used: Model 1, unadjusted; Model 2, adjusted for age, sex, smoking, and body mass index; Model 3, adjusted for age, sex, smoking, body mass index, diabetes, hypertension, old MI, and atrial fibrillation; and Model 4, adjusted for age, sex, smoking, body mass index, diabetes, hypertension, old MI, atrial fibrillation, always use of aspirin, use of clopidogrel at 1 year, always use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB), and revascularization at baseline. Furthermore, we also performed multivariate Cox analysis of MACEs in subgroups. All statistical testing was 2-sided. When $P<.05$, the results were considered statistically significant. Software PASW Statistics (ver. 20.0) was used to perform the analysis.

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Table 1. Baseline clinical characteristics of the study patients according to risk category of always beta-blocker and statin treatment.

	Total	No therapy	beta-Blocker monotherapy	Statin monotherapy	Cotherapy	*P* value
	n=636	n=139	n=71	n=149	n=277	
Age, year	60.42±9.83	59.18±10.55	62.40±9.31	60.71±9.20	60.37±9.87	.217
Male, n (%)	425 (66.8)	96 (69.1)	48 (67.6)	102 (68.5)	179 (64.6)	.772
Heart rate, bpm	69.56±10.16	70.51±9.33	69.72±9.98	70.28±10.00	67.63±10.83	.008
SBP, mm Hg	129.98±17.37	129.37±17.96	132.72±16.68	128.22±17.28	130.53±17.27	.192
DBP, mm Hg	78.21±10.69	78.17±10.61	680.23±10.26	77.32±11.01	78.19±10.66	.271
BMI, kg/m^2	26.08±3.35	26.29±3.23	625.68±3.52	25.78±3.12	26.25±3.50	.294
Smoking, n (%)	331 (52.0)	77 (55.4)	37 (52.1)	73 (49.0)	144 (52.0)	.757
Old MI, n (%)	66 (10.4)	14 (10.1)	10 (14.1)	9 (6.0)	33 (11.9)	.189
Diabetes, n (%)	165 (25.9)	37 (26.6)	20 (28.2)	35 (23.5)	73 (26.4)	.872
Hypertension, n (%)	405 (63.7)	71 (51.1)	49 (69.0)	91 (61.1)	194 (70.0)	.001
Atrial fibrillation, n (%)	21 (3.3)	4 (2.9)	2 (2.8)	4 (2.7)	11 (4.0)	.874
CRE, μmol/L	79.77±19.14	79.54±18.29	81.38±19.21	81.23±19.54	78.68±19.36	.545
UA, μmol/L	304.70±80.08	302.66±81.99	311.52±89.83	307.44±71.54	302.50±81.12	.816
TG, mmol/L	1.69±1.08	1.99±1.45	1.76±1.04	1.51±0.80	1.62±0.98	.010
TC, mmol/L	4.17±1.04	4.37±1.06	4.35±1.20	4.09±1.09	4.08±0.95	.008
LDL, mmol/L	2.36±0.88	2.45±0.89	2.42±0.96	2.33±0.83	2.31±0.89	.281
HDL, mmol/L	1.06±0.27	1.05±0.28	1.07±0.29	1.05±0.24	1.06±0.27	.960
LVEDD, mm	48.02±4.59	48.78±5.10	47.96±4.96	47.74±4.06	47.80±4.48	.282
LVEF,%	62.37±6.58	62.86±6.87	60.26±7.21	62.91±6.28	62.38±6.34	.058
Aspirin, n (%)	612 (96.2)	131 (94.2)	57 (80.3)	149 (100.0)	275 (99.3)	<.001
Clopidogrel, n (%)	453 (71.2)	80 (57.6)	34 (47.9)	115 (77.2)	224 (80.9)	<.001
ACEI or ARB, n (%)	356 (56.0)	67 (48.2)	42 (59.2)	74 (49.7)	173 (62.5)	.013
Revascularization*, n (%)	463 (72.8)	88 (63.3)	48 (67.6)	114 (76.5)	213 (76.9)	.014

Continuous variables are presented as mean±SD; categorical variables are presented as numbers or percentages. ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; BMI – body mass index; CRE – creatinine; DBP – diastolic blood pressure; HDL – high-density lipoprotein; LDL – low density lipoprotein; LVEDD – left ventricle end-diastolic diameter; LVEF – left ventricle ejection fraction; MI – myocardial infarction; SBP – systolic blood pressure; TC – total cholesterol; TG – triglyceride; UA – uric acid. * Included percutaneous coronary intervention and coronary artery bypass grafting.

Results

Baseline Characteristics

A total of 636 patients were included in our study. Table 1 demonstrates the baseline characteristics. Follow-up mean duration was 4.2 years (interquartile range, 4.1-4.4 years). Men were 66.8% of the subjects, who were 25 to 80 years old (mean age: 60.42±9.83 years). No therapy and statin monotherapy groups had a higher heart rate (no therapy, 70.51±9.33 bpm; beta-blocker monotherapy, 69.72±9.98 bpm; statin monotherapy, 70.28±10.00 bpm; cotherapy, 67.63±10.83 bpm; *P*=.008) and a higher percentage of hypertension (no therapy, 51.1%; beta-blocker monotherapy, 69.0%; statin monotherapy, 61.1%; cotherapy, 70.0%; *P*=.001). No therapy and beta-blocker monotherapy groups had higher total cholesterol levels (no therapy,

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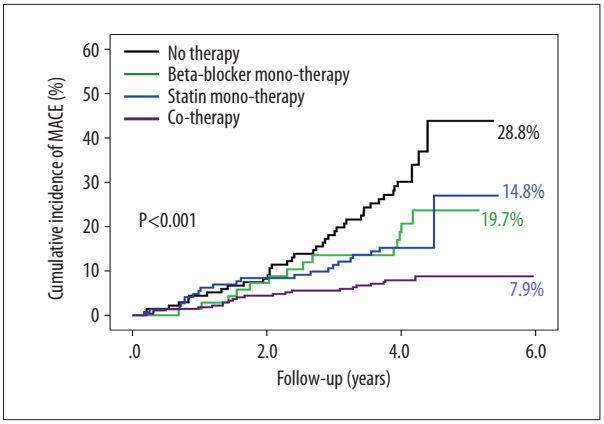

Figure 1. The cumulative incidence of major adverse cardiovascular events (MACEs). Compared with no therapy group, the cumulative incidence of MACEs gradually decreased in the beta-blocker monotherapy group, statin monotherapy group, and cotherapy group (*P*<.001).

4.37±1.06 mmol/L; beta-blocker monotherapy, 4.35±1.20 mmol/L; statin monotherapy, 4.09±1.09 mmol/L; cotherapy, 4.08±0.95 mmol/L; *P*=.008) and triglyceride levels (no therapy, 1.99±1.45 mmol/L; beta-blocker monotherapy, 1.76±1.04 mmol/L; statin monotherapy, 1.51±0.80 mmol/L; cotherapy, 1.62±0.98 mmol/L; *P*=.010). Statin monotherapy and cotherapy groups had higher percentage in the use of aspirin (no therapy, 94.2%; beta-blocker monotherapy, 80.3%; statin monotherapy, 100.0%; cotherapy, 99.3%; *P*<.001); clopidogrel (no therapy, 57.6%; beta-blocker monotherapy, 47.9%; statin monotherapy, 77.2%; cotherapy, 80.9%; *P*<.001); and higher revascularization at baseline (no therapy, 63.3%; beta-blocker monotherapy, 67.6%; statin monotherapy, 76.5%; cotherapy, 76.9%; *P*=.014). The baseline characteristics of subjects presenting MACEs are shown in Supplementary Table 1.

Clinical outcomes

During the follow-up of 4.2±0.3 years, there were 98 (15.4%) MACEs, including zero cardiovascular deaths (0.0%), 8 MIs (1.3%), 73 ischemia-driven revascularizations (11.5%), 17 cases of cardiac function NYHA III or IV (2.7%), and 14 strokes (2.2%). The follow-up data showed the rates of MACEs in the no therapy group, beta-blocker monotherapy group, statin monotherapy group, and cotherapy group were 28.8% (40/139), 19.7% (14/71), 14.8% (22/149), and 7.9% (22/277) (*P*<.001), respectively (Supplementary Table 2). Relative to the no therapy group, the cumulative incidence of MACEs was gradually decreasing in the beta-blocker monotherapy group, statin monotherapy group, and cotherapy group (*P*<.001) (Figure 1). Cumulative event curves of ischemia-driven revascularization were similar to those of MACEs (*P*<.001) (Supplementary Figure 2). Cumulative event curves of MI, progress to NYHA III or IV, and stroke are shown in Supplementary Figure 2.

Table 2. Univariate and multivariate Cox analysis according to risk category of always beta-blocker and statin.

MACE*	No therapy	beta-Blocker monotherapy	Statin monotherapy	Cotherapy
	n=139	n=71	n=149	n=277
Model 1[a]				
HR (95% CI)	1.00	0.66 (0.36–1.21)	0.50 (0.30–0.84)	0.25 (0.15–0.43)
P value		.175	.009	<.001
Model 2[b]				
HR (95% CI)	1.00	0.66 (0.36–1.22)	0.50 (0.30–0.85)	0.26 (0.15–0.43)
P value		.185	.010	<.001
Model 3[c]				
HR (95% CI)	1.00	0.63 (0.34–1.16)	0.48 (0.28–0.80)	0.24 (0.14–0.41)
P value		.139	.006	<.001
Model 4[d]				
HR (95% CI)	1.00	0.59 (0.31–1.09)	0.35 (0.20–0.60)	0.16 (0.09–0.28)
P value		.092	<.001	<.001

CI – confidence interval; HR – hazard ratio; MACE – major adverse cardiac events. * HR and *P* values are based on comparison with the no therapy group; [a] Model 1: Unadjusted; [b] Model 2: Multivariate adjustment was made for age, sex, smoking, body mass index; [c] Model 3: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation; [d] Model 4: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation, always use of aspirin, use of clopidogrel at 1 year, always use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, revascularization at baseline.

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Table 3. Multivariate Cox analysis of MACE in subgroups.

MACE	beta-Blocker monotherapy *vs.* Cotherapy*		Statin monotherapy *vs.* Cotherapy**	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Model 1[a]	0.39 (0.20–0.76)	.005	0.51 (0.28–0.92)	.025
Model 2[b]	0.39 (0.20–0.77)	.006	0.50 (0.28–0.91)	.023
Model 3[c]	0.37 (0.19–0.73)	.004	0.52 (0.29–0.95)	.034
Model 4[d]	0.28 (0.13–0.59)	.001	0.54 (0.29–0.98)	.044

CI – confidence interval; HR – hazard ratio; MACE – major adverse cardiac event. * HR and *P* values are based on comparison with beta-blocker monotherapy group; ** HR and *P* values are based on comparison with statin monotherapy group; [a] Model 1: Unadjusted; [b] Model 2: Multivariate adjustment was made for age, sex, smoking, body mass index; [c] Model 3: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation; [d] Model 4: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation, always use of aspirin, use of clopidogrel at 1 year, always use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, revascularization at baseline.

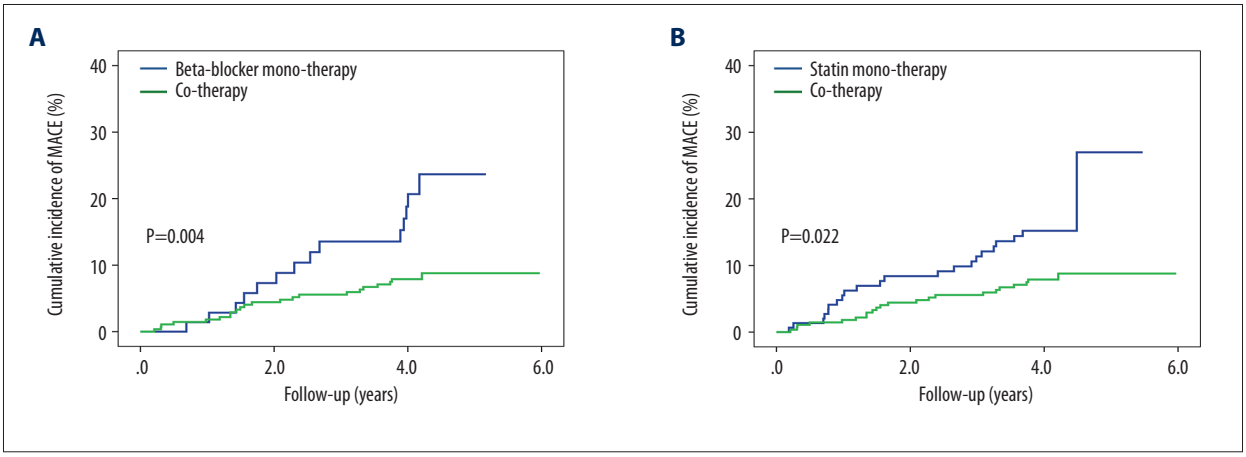

Figure 2. The cumulative incidence of major adverse cardiovascular events (MACEs) in the subgroup. (**A**) Patients in the cotherapy group showed a lower MACE occurrence than the beta-blocker monotherapy group (*P*=.004). (**B**) Patients in the cotherapy group showed a lower MACE occurrence than the statin monotherapy group (*P*=.022).

Univariate and multivariate Cox regression models were used to reveal the impact of consistent beta-blocker and statin treatment on MACEs in ACS patients. In univariable Cox regression model (Model 1), compared with no therapy group, the hazard ratios (HRs) for MACEs in the statin monotherapy group and the cotherapy group were 0.50 (95% confidence interval 0.30–0.84, *P*=.009) and 0.25 (95% CI 0.15–0.43, *P*<.001). Multivariate analysis indicated that the statin monotherapy group and the cotherapy group had a lower risk of MACEs than the no therapy group (Model 2, statin monotherapy group, HR 0.50, 95% CI 0.30–0.85, *P*=.010; cotherapy group, HR 0.26, 95% CI 0.15–0.43, *P*<.001; Model 3, statin monotherapy group, HR 0.48, 95% CI 0.28–0.80, *P*=.006; cotherapy group, HR 0.24, 95% CI 0.14–0.41, *P*<.001; Model 4, statin monotherapy group, HR 0.35, 95% CI 0.20–0.60, *P*<.001; cotherapy group, HR 0.16, 95% CI 0.09–0.28, *P*<.001; compared with the no therapy group). There was no significant difference the relative risk of MACEs between the no therapy group and the beta-blocker monotherapy group (Table 2).

Furthermore, relative to the no therapy group, the statin monotherapy group and the cotherapy group showed a lower risk of ischemia-driven revascularization and cardiac function NYHA III or IV progression. There were no cardiovascular deaths, 8 MIs, and 14 strokes during the follow-up. The incidence of cardiovascular death, MI, and stroke was low and did not allow for further analysis (Supplementary Tables 3, 4).

Subgroup analysis

We also conducted a subgroup analysis between groups. In the univariate Cox regression model (Model 1), the cotherapy group showed a lower MACE occurrence than the beta-blocker monotherapy group (HR 0.39, 95% CI 0.20–0.76, *P*=.005).

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Further variables were adjusted for in Model 2, Model 3, and Model 4, and there were no significant changes of HR for MACEs in the cotherapy group (Model 2, HR 0.39, 95% CI 0.20–0.77, *P*=.006; Model 3, HR 0.37, 95% CI 0.19–0.73, *P*=.004; Model 4, HR 0.28, 95% CI 0.13-0.59, *P*=.001) (Table 3, Figure 2A).

In addition, relative to the statin monotherapy group, the cotherapy group showed a significant 49% reduction in MACE occurrence (HR 0.51, 95% CI 0.28–0.92, *P*=.025). This reduction of MACEs was not attenuated when adjusting for addition variables in Model 2, Model 3, and Model 4 (Model 2, HR 0.50, 95% CI 0.28–0.91, *P*=.023; Model 3, HR 0.52, 95% CI 0.29–0.95, *P*=.034; Model 4, HR 0.54, 95% CI 0.29–0.98, *P*=.044) (Table 3, Figure 2B).

Discussion

In this observational cohort study, we found that combination therapy with a beta-blocker and a statin lowered MACE occurrence in patients with ACS. This combination therapy also showed benefits in inhibiting ischemia-driven revascularization and NYHA III or IV cardiac function progression. In subgroup analysis, the combination therapy also significantly reduced MACE occurrence in ACS patients, compared with beta-blocker or statin monotherapy alone.

Previous studies showed that combination therapy with a beta-blocker and a statin was beneficial in lowering short-term MACEs in patients with coronary arterial disease [10–12,16,17]. Combination therapy application at an early stage was suggested to be correlated with reduced mortality and morbidity in patients with MI complicated with heart failure [10]. Moreover, this combination therapy could also reduce stroke after coronary artery bypass graft [16]. These findings were in accordance with and further supported our results showing that patients that received combination therapy had a lower MACE occurrence.

To strengthen our conclusion, we used multivariate Cox proportional hazards regression to assess the power of combination therapy to reduce adverse outcomes of ACS. To remove the drug effect, we followed patients closely and assessed drug treatment throughout the entire follow-up period. We also used several Cox proportional hazards regression models (Models 1–4) to assess the relationship between combination therapy and the risk of adverse outcomes in ACS patients. All the analyses indicated that combination therapy decreased MACE occurrence in ACS patients.

The combination of treatments has more potent beneficial effects on MACEs than monotherapy. The mechanisms underlying the beneficial effects of cotherapy were uncertain. Statins and beta-blockers exert differing effects on the heart and vasculature. Statins are important drugs that decrease cardiovascular events by increased scavenging of reactive oxygen species; they also attenuate coronary artery plaque inflammation, have antithrombotic effects, and decrease endothelial cell apoptosis [18,19]. These properties of statins all play roles in stabilizing vulnerable coronary plaques, and thereby reduce patient vulnerability to acute ischemic events. Our results showed that a beneficial effect on MACEs was observed in statin monotherapy. This finding may indicate that statin administration is independently associated with a reduced incidence of MACEs even in the presence of beta-blockers. Beta-blockers are associated with lower myocardial oxygen, anti-inflammatory effects, and a shift in energy metabolism [20]. Moreover, previous studies showed that beta-blockers can also reduce the rate of progression of carotid intima-media thickness and seem to have antiatherogenic properties [21,22]. These properties of beta-blockers may reinforce the effect of statins on vulnerable plaques. Therefore, combination therapy with a beta-blocker and a statin may coordinate to reduce occurrences of MACE in ACS.

Limitations

Our study had some limitations. Subjects enrolled were from a single center, which was limited to the native Chinese population. In addition, 6.3% of subjects were lost to follow-up, which could result in biases. These facts may limit generalizing our findings.

Conclusions

Results from our current study indicated that using beta-blocker and statin combination therapy lowered the risk of MACEs in ACS patients.

Ethics Statement

Protocols of this investigation were reviewed and approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

Acknowledgments

We appreciate the help and support of all the participants involved in the study.

Conflict of interests

None.

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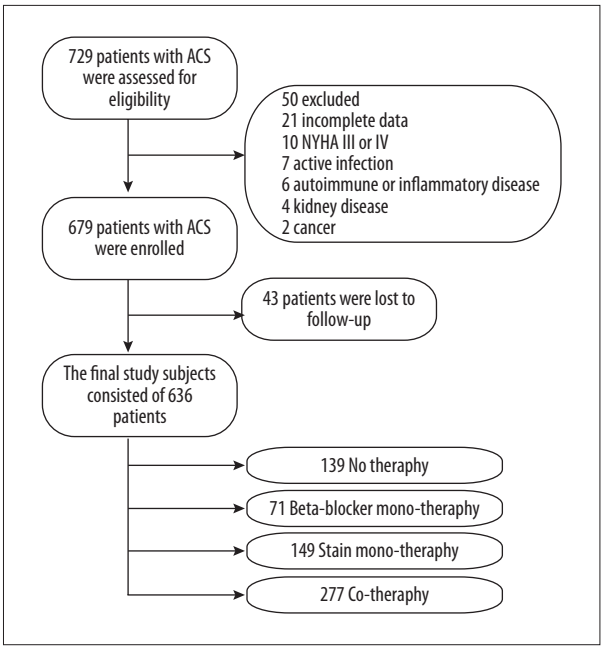
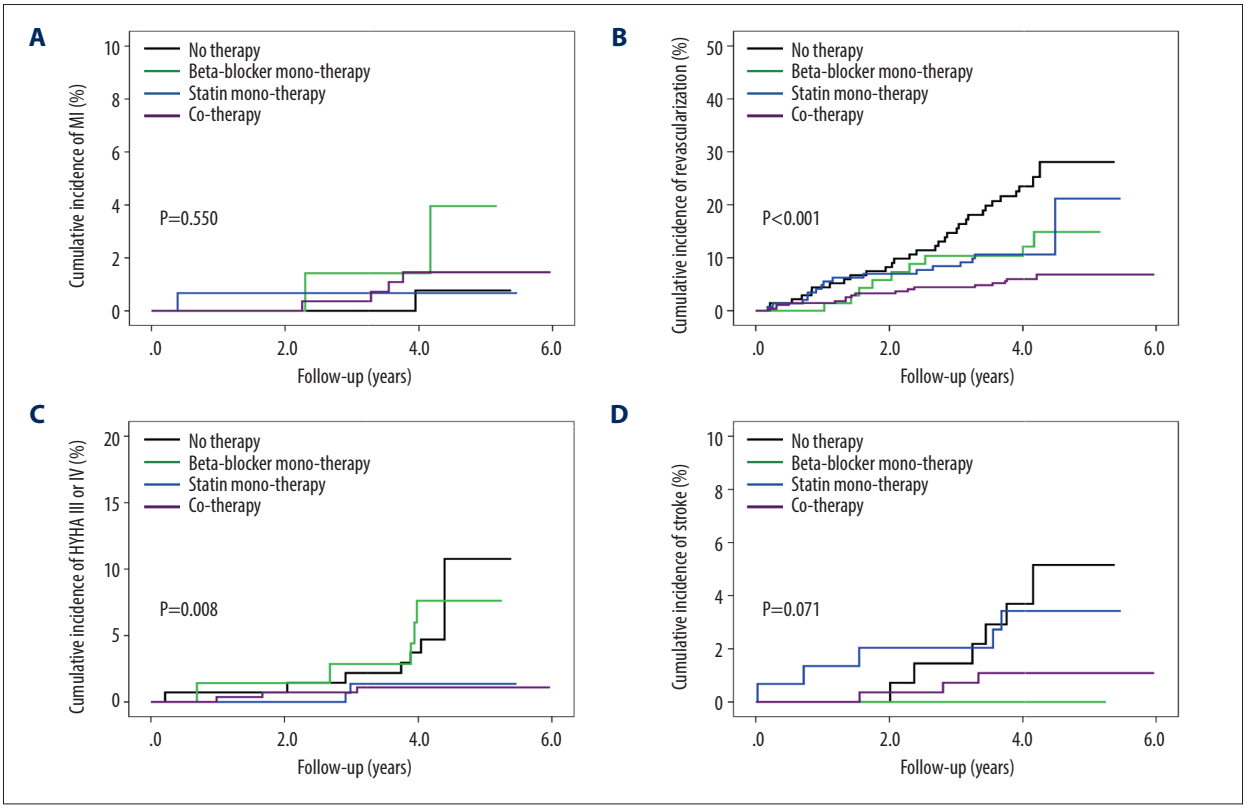
Supplementary Data



Supplementary Figure 1. Patient flowchart.



Supplementary Figure 2. The cumulative incidence of myocardial infarction (**A**), ischemia-driven revascularization (**B**), progress to New York Heart Association (NYHA) III or IV (**C**), and stroke (**D**). There were 0 cardiovascular deaths, which did not allow for Kaplan-Meier analysis.

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Supplementary Table 1. Baseline clinical characteristics of patients with MACE.

	Total	MACE (+)	MACE (–)	P value
	n=636	n=98	n=538	
Age, year	60.42±9.83	59.97±9.28	60.50±9.93	0.584
Male, n%	425 (66.8)	69 (70.4)	356 (66.2)	0.484
Heart rate, bpm	69.56±10.16	69.77±10.36	68.42±9.00	0.206
SBP, mmHg	129.98±17.37	129.38±18.35	130.09±17.20	0.812
DBP, mmHg	78.21±10.69	78.01±9.69	78.25±10.87	0.802
BMI, kg/m^2	26.08±2.93	26.11±2.80	26.07±2.95	0.582
Smoking, n%	331 (52.0)	54 (55.1)	277 (51.5)	0.583
Old MI, n%	66 (10.4)	9 (9.2)	57 (10.6)	0.857
Diabetes, n%	165 (25.9)	23 (23.5)	142 (26.4)	0.617
Hypertension, n%	405 (63.7)	66 (67.3)	339 (63.0)	0.427
Atrial fibrillation, n%	21 (3.3)	2 (2.0)	19 (3.5)	0.757
CRE, umol/L	79.77±19.14	79.18±15.79	79.88±19.71	0.725
UA, umol/L	304.70±80.08	299.38±79.21	305.67±80.28	0.627
TG, mmol/L	1.69±1.08	1.71±0.99	1.69±1.10	0.532
TC, mmol/L	4.17±1.04	4.27±1.07	4.16±1.04	0.241
LDL, mmol/L	2.36±0.88	2.45±0.85	2.34±0.89	0.131
HDL, mmol/L	1.06±0.27	1.03±0.25	1.06±0.27	0.308
LVEDD, mm	48.02±4.59	48.40±4.74	47.94±4.57	0.537
LVEF,%	62.37±6.58	62.51±6.94	62.35±6.51	0.877
Aspirin, n%	612 (96.2)	96 (98.0)	516 (95.9)	0.562
clopidogrel, n%	453 (71.2)	78 (79.6)	375 (69.7)	0.052
ACEI or ARB, n%	356 (56.0)	53 (54.1)	303 (56.3)	0.740
Revascularization*, n%	463 (72.8)	81 (82.7)	382 (71.0)	0.019

Continuous variables are presented as mean±SD; categorical variables are presented as numbers or percentages. ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blocker; BMI – body mass index; CRE – creatinine; SBP – systolic blood pressure; DBP – diastolic blood pressure; HDL – high-density lipoprotein; LDL – low density lipoprotein; LVEDD – left ventricle end-diastolic diameter; LVEF – left ventricle ejection fraction; MI – myocardial infarction; SBP – systolic blood pressure; TC – total cholesterol; TG – triglyceride; UA – uric acid. * Included percutaneous coronary intervention and coronary artery bypass grafti.

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Supplementary Table 2. MACE of the study patients according to risk category of always beta-blocker and statin treatment.

	Total	No therapy	Beta-blocker mono-therapy	Statin mono-therapy	Co-therapy	*P* value
	n=636	n=139	n=71	n=149	n=277	
MACE	98 (15.4)	40 (28.8)	14 (19.7)	22 (14.8)	22 (7.9)	<0.001
Cardiovascular death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
Myocardial infarction, n (%)	8 (1.3)	1 (0.7)	2 (2.8)	1 (0.7)	4 (1.4)	0.531
Ischemia-driven revascularization*, n (%)	73 (11.5)	31 (22.3)	9 (12.7)	16 (10.7)	17 (6.1)	<0.001
Progress to NYHA III or IV, n (%)	17 (2.7)	7 (5.0)	5 (7.0)	2 (1.3)	3 (1.1)	0.008
Stroke, n (%)	14 (2.2)	6 (4.3)	0 (0)	5 (3.4)	3 (1.1)	0.071

* Included percutaneous coronary intervention and coronary artery bypass grafting. MACE – major adverse cardiac events; NYHA – New York Heart Association.

Supplementary Table 3. Multivariate COX analysis of ischemia-driven revascularization according to risk category of always beta-blocker and statin treatment.

Ischemia-driven revascularization#	No therapy	beta-Blocker mono-therapy	Statin mono-therapy	Co-therapy
	n=139	n=71	n=149	n=277
Model 1[a]				
HR* (95% CI)	1.00	0.55 (0.26–1.15)	0.48 (0.26–0.87)	0.26 (0.14–0.47)
*P** value		0.114	0.016	<0.001
Model 2[b]				
HR* (95% CI)	1.00	0.56 (0.26–1.18)	0.48 (0.26–0.88)	0.26 (0.15–0.48)
*P** value		0.128	0.017	<0.001
Model 3[c]				
HR* (95% CI)	1.00	0.55 (0.26–1.16)	0.45 (0.24–0.83)	0.25 (0.14–0.46)
*P** value		0.115	0.010	<0.001
Model 4[d]				
HR* (95% CI)	1.00	0.46 (0.22–0.99)	0.29 (0.15–0.54)	0.14 (0.08–0.26)
*P** value		0.047	<0.001	<0.001

***** Compared with the no therapy group; [a] Model 1: Unadjusted; [b] Model 2: Multivariate adjustment was made for age, sex, smoking, body mass index; [c] Model 3: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation; [d] Model 4: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation, always use of aspirin, use of clopidogrel at 1 year, always use of ACEI or ARB, revascularization at baseline; # included percutaneous coronary intervention and coronary artery bypass grafting. There were 0 cardiovascular death, 8 myocardial infarction, and 14 stroke during the follow-up. The incidence of cardiovascular death, myocardial infarction, and stroke were low and did not allow for further analysis. CI – confidence interval; HR – hazard ratio.

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Supplementary Table 4. Multivariate COX analysis of progress to NYHA III or IV according to risk category of always β-blocker and statin treatment.

Progress to NYHA III or IV	No therapy	beta-Blocker mono-therapy	Statin mono-therapy	Co-therapy
	n=139	n=71	n=149	n=277
Model 1[a]				
HR* (95% CI)	1.00	1.36 (0.43–4.30)	0.26 (0.06–1.27)	0.21 (0.05–0.80)
*P** value		0.598	0.097	0.023
Model 2[b]				
HR* (95% CI)	1.00	1.18 (0.37–3.77)	0.25 (0.05–1.21)	0.20 (0.05–0.76)
*P** value		0.785	0.085	0.018
Model 3[c]				
HR* (95% CI)	1.00	1.05 (0.32–3.38)	0.24 (0.05–1.18)	0.17 (0.04–0.65)
*P** value		0.942	0.080	0.010
Model 4[d]				
HR* (95% CI)	1.00	1.04 (0.32–3.38)	0.24 (0.05–1.23)	0.17 (0.04–0.68)
*P** value		0.952	0.088	0.013

* Compared with the no therapy group; [a] Model 1: Unadjusted; [b] Model 2: Multivariate adjustment was made for age, sex, smoking, body mass index; [c] Model 3: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation; [d] Model 4: Multivariate adjustment was made for age, sex, smoking, body mass index, diabetes, hypertension, old myocardial infarction, atrial fibrillation, always use of aspirin, use of clopidogrel at 1 year, always use of ACEI or ARB, revascularization at baseline. There were 0 cardiovascular death, 8 myocardial infarction, and 14 stroke during the follow-up. The incidence of cardiovascular death, myocardial infarction, and stroke were low and did not allow for further analysis. CI – confidence interval; HR – hazard ratio.

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