Long-term effects of nicorandil combined with dihydropyridine calcium channel blockers on cardiovascular outcomes in patients with coronary heart disease: a real-world observational study

Running title: Nicorandil combined with DHP-CCBs in CHD

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Abstract

Objective: To investigate whether the addition of nicorandil to dihydropyridine calcium channel blockers (DHP-CCBs) can lower the occurrence of major adverse cardiovascular events (MACE) in patients with coronary heart disease (CHD).

Methods: A multicenter, retrospective, real-world study was conducted. Between August 2002 and March 2020, a total of 7,413 eligible CHD patients were classified into DHP-CCBs plus nicorandil combination (n = 1,843) and DHP-CCBs (n = 5,570) treatment groups. The primary outcome was MACE, defined as a composite of myocardial infarction, stroke, and all-cause mortality. Propensity score matching was used to adjust for confounding factors.

Results: After propensity score matching, combination therapy was associated with a reduced risk of MACE (HR: 0.80, 95% CI: 0.67–0.97). The combination group also experienced a reduced risk of stroke (HR: 0.55, 95% CI: 0.44–0.69), but not myocardial infarction (HR: 1.21, 95% CI: 0.91–1.61) or all-cause mortality (HR: 1.24, 95% CI: 0.63–2.44). Subgroup analysis disclosed that the benefits of the combined treatment on MACE were more pronounced in diabetic than in non-diabetic patients.

Conclusions: The combination of nicorandil and DHP-CCBs may be more beneficial than DHP-CCBs alone in reducing long-term risks of MACE and stroke in patients with CHD.

Significance Statement

This retrospective study reviewed the databases of two tertiary hospitals in Wuhan, China. A total of 137,714 CHD patient records were reviewed. We compared the clinical outcomes of patients who were treated with DHP-CCBs alone versus patients who were treated with both nicorandil and DHP-CCBs. By using the propensity score matching method to match the baseline characteristics of different treatment groups, we found that the 3-year incidence rate of MACE in patients treated with nicorandil and DHP-CCBs was relatively lower compared to patients treated with DHP-CCBs alone. The combination of nicorandil and DHP-CCBs may be more beneficial than DHP-CCBs used alone in reducing long-term risks of MACE in patients with CHD.

Keywords: coronary heart disease; angina; nicorandil; calcium channel blockers; major adverse cardiovascular events

Introduction

Coronary heart disease (CHD) is characterized by chronic or acute myocardial ischemia caused by stenosis of the coronary artery lumen that leads to the typical symptoms of angina [1, 2]. Antiplatelet agents, anti-anginal drugs, and statins are cornerstones of the treatment of CHD, while revascularization is indicated for acute coronary syndrome (ACS) [3-6]. Despite recent improvements in diagnosis and treatment, CHD remains a leading etiology of cardiovascular morbidity and mortality worldwide [7, 8]. Patients with CHD are at higher risk for the long-term incidence of major adverse cardiovascular events (MACE), which typically include myocardial infarction (MI), stroke, and mortality [9].

Calcium channel blockers (CCBs) are commonly used to treat hypertension and angina [10, 11]. Because of their contrasting chemistry and pharmacodynamics, CCBs may be classified into two categories, dihydropyridine (DHP) and non-DHP CCBs [12]. Both DHP-CCBs and non-DHP CCBs may be used to treat coronary spasm, while DHP-CCBs are more commonly used than non-DHP CCBs in patients with CHD. Through the noncompetitive blocking of L-type calcium channels in cardiac and smooth muscle membranes, DHP-CCBs dilate coronary and systemic vasculature, thereby improving coronary perfusion and reducing blood pressure [6, 13]. However, despite the aforementioned benefits, only a few clinical trials have shown benefits of DHP-CCBs on cardiovascular outcomes in patients with stable CHD [14-17].

Nicorandil is a nitrate-moiety nicotinamide ester that is widely used to treat angina [18]. As an adenosine-sensitive potassium (K(ATP)) channel opener, its mechanism of action is distinct from those of CCBs [19]. Nicorandil stimulates cyclic guanosine monophosphate production, activates K^+ ion channels, and promotes K^+ ion outflow in vascular smooth muscle cells, thereby improving coronary blood flow, particularly in the coronary microcirculation [20]. In addition to its proven clinical efficacy in alleviating the symptoms of angina, nicorandil may reduce the risks of MACE and mortality in patients with CHD [21, 22]. In view of the increasing prevalence of patients with CHD who take nicorandil and DHP-CCBs concurrently, determining the effect of combining nicorandil with DHP-CCBs on the long-term incidence of MACE in patients with CHD is imperative. Therefore, in this real-world study, we aimed to analyze the long-term effects of the combination of nicorandil and DHP-CCBs compared to DHP-CCBs alone on MACE incidence in CHD patients.

Methods

Ethical approval was obtained from Tongji Hospital affiliated with Huazhong University of Science and Technology Tongji Medical College (approval number TJ-IRB201909112). We followed the most recent version of the Declaration of Helsinki and the *Guidelines for Good Epidemiology Practices* during the design and conduction of our study. The study protocol was registered in the Chinese clinical trial registry, with the validated registration number of *ChiCTR1900027812*. The

requirement for informed consent was waived due to the retrospective study design.

Study design and participants

We conducted a real-world retrospective cohort study that evaluated CHD patients hospitalized in two tertiary healthcare institutions (Tongji Hospital affiliated with Huazhong University of Science and Technology Tongji Medical College, and Union Hospital affiliated with Huazhong University of Science and Technology Tongji Medical College) in Wuhan, China between August 2002 and March 2020. Inclusion criteria included age of 18 years or older; hospitalized for the treatment of CHD; treated with DHP-CCBs with or without nicorandil at discharge; and the availability of more than two sets of admission records. Exclusion criteria consisted of asymptomatic myocardial ischemia; cardiovascular conditions other than CHD (e.g., dilated, hypertrophic, or restrictive cardiomyopathies; cardiac amyloidosis; and congenital heart disease); histories of cardiac transplants or valve surgery.

Data extraction

The methodology of data extraction has been reported in detail previously [23]. In brief, pre-trained researchers collected medical information according to a predefined data extraction table from the various electronic medical record (EMR) systems in the participating medical centers. The primary medical electronic systems included the EMR for demographic characteristics, hospital registration date, date of diagnosis, and surgical records; the healthcare information system (HIS) for medical

administrative data; and the laboratory information system for laboratory findings. Subsequently, the following data were extracted for each patient: (1) demographic characteristics, including age, sex, smoking history, and previous histories of revascularization (percutaneous coronary intervention (PCI) and/or coronary artery bypass graft); (2) comorbidities and past medical histories of conditions such as hypertension, diabetes mellitus, hyperlipidemia, angina (stable or unstable), MI, ACS, and heart failure; (3) concurrent cardiovascular medications including antiplatelet agents, nitrates, beta-adrenergic receptor blockers (BBs), nicorandil, DHP-CCBs, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and statins. Diagnoses of CHD and comorbidities were established during the hospitalization of each patient according to relevant clinical guidelines.

Clinical outcomes

The primary outcome was the rate of MACE at the 3-year follow-up, defined as a composite outcome of MI, stroke, and all-cause mortality. Secondary outcomes were rates of individual components of MACE at the 3-year follow-up.

Statistical analyses

Continuous variables were summarized as mean values and standard deviations (SD), and categorized variables were shown as frequencies and percentages. The Intergroup differences were examined with the two-sample Student t-test or

Wilcoxson test, and the chi-squared test or Fisher's exact probability test, respectively. Rates of primary and secondary outcomes were analyzed by Kaplan-Meier survival curves and the log-rank test, and presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Additionally, the incidence density of MACE and its components (per 1000 person-years) based on the number of events divided by the number of person-years of follow-up were estimated by using exact Poisson limits.

Subsequently, a propensity score matching (PSM) method was applied to minimize the potential influence of confounding factors. The details of the PSM method have been reported in detail [23]. Variables included age; sex; smoking; history of revascularization; comorbidities (diabetes mellitus, hypertension, hyperlipidemia, ACS, stable angina, and unstable angina); and concomitant medications (including antiplatelet drugs, nitrates, BBs, ACEI/ARBs, MRAs, and statins).

The stabilities of findings were subjected to sensitivity analyses performed by a restriction to patients admitted after nicorandil became available in China and by utilizing PSM trimming (trimming the propensity score distribution below the 5^{th} percentile and above the 95^{th} percentile). To assess the influence of unmeasured confounding factors, E-values were calculated as previously reported [24]. In addition, subgroup analyses of the association between combined therapy and MACE were conducted based on predefined variables, which included age, sex, a

diagnosis of ACS, smoking status; and the comorbidities of diabetes, hypertension, and hyperlipidemia. SAS 9.4 software (SAS Institute Inc, Cary, NC, USA) was used for statistical analysis, and $P < 0.05$ indicated statistical significance.

Results

Baseline characteristics

The patient screening and inclusion algorithm is shown in **Figure 1**. Briefly, 137,714 patients were screened based on the HIS and EMR systems, and 130,301 patients were excluded for the reasons listed in **Figure 1**. A total of 7,413 patients were included in the final analysis. Of these, 1,843 patients were treated with both DHP-CCBs and nicorandil (combination group), while 5,570 patients were treated with DHP-CCBs without nicorandil (DHP-CCBs group). The baseline characteristics of the two groups are shown in **Table 1**. Before PSM, patients in the combination group were more likely to be male (64.5% vs. 61.4%, $P = 0.020$) and current smokers (22.7% vs. 20.2%, $P = 0.032$), whereas the DHP-CCBs group displayed higher prevalence rates of diabetes (44.6% vs. 38.5%, $P < 0.001$), hypertension (93.4% vs. 87.0%, $P < 0.001$), and hyperlipidemia (30.5% vs. 15.8%, $P < 0.001$). Mean age and prevalence rates of previous coronary revascularization and heart failure were similar between the two groups. After PSM for the entire population, the baseline characteristics were well balanced between two groups (all $P > 0.05$), which included 1,315 patients in each group.

Clinical outcomes

The median follow-up duration for the entire population was 8.3 months (interquartile range [IQR]: 1.7–18 months). Of the total cohort, the combination group experienced significantly lower risks of MACE at 3-year of follow-up (HR: 0.65, 95% CI: 0.57–0.73, $P < 0.0001$; **Figure 2A**) and stroke (HR: 0.41, 95% CI: 0.35–0.48, $P < 0.0001$; **Figure 2B**), whereas the risks of MI ($P = 0.2941$; **Figure 2C**) and all-cause mortality were similar between groups ($P = 0.1856$; **Figure 2D**). Similarly, compared to the DHP-CCBs group, the combination group displayed lower incidence densities of MACE and stroke, while the incidence densities of MI and all-cause mortality were similar (**Table 2**). After PSM, the risks of MACE (HR: 0.80, 95% CI: 0.67–0.97, $P = 0.0193$; **Figure 3A**) and stroke (HR: 0.55, 95% CI: 0.44–0.69, $P < 0.0001$; **Figure 3B**) were lower in the combination group, while the risks of MI (HR: 1.21, 95% CI 0.91–1.61, $P = 0.1845$; **Figure 3C**) and all-cause mortality (HR: 1.24, 95% CI 0.63–2.44, $P = 0.5283$; **Figure 3D**) were similar.

Sensitivity and subgroup analyses

Results of sensitivity analyses based on PSM with trimming and limitation to patients hospitalized after nicorandil availability in China are shown in **Table 3**. Both sensitivity analyses indicated that the combination group experienced a reduced incidence of MACE and stroke as compared to the DHP-CCBs group (all $P < 0.05$). In addition, sensitivity analyses showed similar incidence rates of MI and all-cause mortality between the two groups (all $P > 0.05$, **Table 3**). The E-values for the

sensitivity analyses using PSM trimming or limited to patients admitted after nicorandil availability in China were 1.78 and 1.89 for 3-year MACE-free survival rates, respectively, and were both 2.99 for stroke-free survival rates. The E-values reflected the robustness of the findings.

In addition, multiple predefined subgroup analyses showed no significant interactions between demographic and clinical characteristics such as age, sex, diagnosis of ACS, smoking status, hypertension, and hyperlipidemia on the benefits of nicorandil combined with DHP-CCBs on the incidence of MACE (**Figure 4**, all *P* for subgroup interactions > 0.05). However, the subgroup analysis suggested that comorbid diabetes may have significantly affected the effectiveness of the combined nicorandil and DHP-CCBs. The benefits of the combined treatment on MACE were more pronounced in diabetic compared to the non-diabetic patients (HR 0.66 versus 0.96, *P* for subgroup interaction = 0.043; **Figure 4**).

Discussion

In this real-world multicenter retrospective cohort study, we included 7,413 CHD patients, and showed that compared to DHP-CCBs alone, treatment that combined nicorandil and DHP-CCBs was associated with a significantly reduced incidence of MACE during the three years of follow-up. Subsequent analysis according to the components of MACE showed that, combined treatment was associated with a significantly reduced risk of stroke, but not for the incidence of MI or all-cause

mortality. These results were consistent after PSM to minimize the influences of potential confounding factors. Moreover, the stability of the findings was further validated in sensitivity analyses. Finally, consistent results were obtained in most of the subgroup analyses except for subgroup analysis according to the diabetic status, which showed a more pronounced benefit of the combined treatment on MACE in diabetic than in non-diabetic patients. Taken together, our findings suggest that the combination of nicorandil and DHP-CCBs may be more beneficial than DHP-CCBs alone in reducing the long-term risk of MACE and stroke in patients with CHD. These findings support the combined use of nicorandil and DHP-CCBs in patients with CHD.

As a real-world observational study, our analysis included all available CHD patients who met the inclusion criteria without limitations of disease severity, which enhanced the applicability of the results to daily clinical practice. DHP-CCBs dilate coronary arteries, which may confer an additional benefit in the treatment of angina [25]. Moreover, in view of the contrasting pharmacodynamics and efficacies of DHP- and non-DHP CCBs, we only included patients treated with DHP-CCBs to minimize potential confounding variables. Although many CHD patients, particularly those with hypertension, use DHP-CCBs, their effects on clinical outcomes are not fully determined [25]. The Coronary disease Trial Investigating Outcome with Nifedipine (ACTION) trial demonstrated that long-acting nifedipine reduced the incidence of coronary angiography and cardiovascular interventions in

stable CHD, but failed to improve MACE-free survival [16]. Similarly, nifedipine did not improve the composite outcome of cardiac death, nonfatal MI, and unstable angina when compared to atenolol in the Total Ischaemic Burden European Trial (TIBET) [26]. Accordingly, for patients with CHD using DHP-CCBs, combined treatment is reasonable.

Current European Society of Cardiology guidelines propose that as a nitrate derivative of nicotinamide, nicorandil has anti-anginal effects similar to those of nitrates or beta-blockers, which may improve the symptoms of patients with CHD, particularly those with microvascular dysfunction [4]. Increasing evidence has indicated the potential benefits of nicorandil on cardiovascular outcomes. In the landmark Impact of Nicorandil in Angina (IONA) trial, nicorandil significantly reduced the incidence of MACE when compared to placebo in CHD patients with the concomitant use of anti-anginal agents including CCBs [27]. In the subsequent Japanese Coronary Artery Disease (JCAD) study, nicorandil reduced all-cause mortality when compared to a propensity-matched control group of patients with stable angina [28]. Moreover, in view of the potential benefit of nicorandil on microvascular function, the combination of nicorandil with other anti-anginal drugs, such as DHP-CCBs, is likely synergistic [29]. However, few studies have evaluated the efficacy of nicorandil on stroke risk reduction in patients with CHD. Our study showed that compared to DHP-CCBs, combined treatment with nicorandil and DHP-CCBs was associated with a significantly reduced incidence of MACE and the

component event of stroke in patients with CHD. A rat model demonstrated that during subacute ischemic stroke, nicorandil improved neurobehavioral and motor function and reduced the size of ischemic lesions [30]. Moreover, preclinical studies suggest a neuroprotective role of nicorandil through attenuation of neuroinflammation during cerebral ischemic injury [31-33]. Further studies are needed to validate our findings and to determine the molecular mechanisms underlying the benefits of nicorandil on stroke.

In this study, subgroup analysis showed that the benefit of the combined treatment on MACE may be more pronounced in diabetic patients as compared to non-diabetic patients. Although the mechanisms underlying the results of the subgroup analysis remain to be clarified, these findings are important because diabetes is an independent predictor of severe CHD [34, 35]. Prospective clinical studies should be considered to validate the potential benefits of nicorandil in diabetic patients with CHD.

This study had several limitations. First, because of its observational study design, the results could not establish a causal relationship between the combined treatment and the reduced incidence of MACE and stroke. However, our findings strongly support the conduction of a prospective clinical trial for further validation. A second limitation was its retrospective design. Although we screened consecutive CHD patients from two medical centers for eligibility, recall and selection biases may have

confounded the results. Third, as this was a real-world retrospective study, patient diagnoses were based on information in the medical record at discharge. Patients with signs and symptoms of ischemia and no obstructive coronary artery disease (INOCA) were not included. Therefore, we were unable to evaluate the effect of these drugs on patients with INOCA in this study. Future studies should be considered for further investigation. Moreover, because we restricted inclusion to patients who used nicorandil and DHP-CCBs concurrently, we were unable to determine the effects of combining nicorandil with non-DHP CCBs on clinical outcomes. Future clinical studies are necessary to evaluate the efficacy of nicorandil-non-DHP CCB combinations. In addition, although we applied PSM analysis to minimize the influences of the potential confounding factors on outcomes, there may have been unidentified and thereby unadjusted factors that may have affected the results. For example, the prevalence of atrial fibrillation (AF) may affect the risk of stroke and therefore confound results. However, we were unable to determine the influence of AF because this variable was not extracted. Similarly, the influences of body mass index and alcohol intake on the results could not be determined because these variables were also not extracted. Moreover, although a diagnosis of CHD was an inclusion criterion, cases may have been missed in a real-world context due to the use of alternative diagnostic codes. Finally, the follow-up duration was limited to three years. Prospective studies with longer follow-up durations should be performed to validate the long-term effectiveness of the combined treatment in CHD patients.

Conclusions

Nicorandil combined with DHP-CCBs may be more effective than DHP-CCBs alone in reducing the long-term risks of MACE and stroke in patients with CHD. Moreover, the effectiveness of the combined treatment may be more pronounced in patients with comorbid diabetes. Although the results should be validated in large-scale clinical trials, these findings support the combined use of nicorandil and DHP-CCBs in patients with CHD.

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Conflict of interest disclosure

The authors have no conflicts of interest to declare.

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Ethics approval statement

Ethical approval was obtained from Tongji Hospital affiliated with Huazhong University of Science and Technology Tongji Medical College (approval number TJ-IRB201909112).

Data Availability Statement

The data that support the findings of this study are available from the corresponding

author upon reasonable request.

Author contributions

Ning Zhou contributed to the study conception, design, and data interpretation; and revised the manuscript critically for important intellectual content. Jia Cheng, Zixuan Zhang, and Hongyang Shu analyzed and interpretated data and made substantial contributions to the writing of the manuscript. Weijian Hang, Qingqing Zhao, Jinzhao Zhao, and Zhihao Xiao acquired clinical data and reviewed it critically for important intellectual content. All authors approved the final manuscript for submission.

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Figure legends

Figure 1 Flowchart of patient inclusion and exclusion.

CHD, coronary heart disease; DHP-CCBs, dihydropyridine calcium channel blockers; EMR, electronic medical record; HIS, healthcare information system.

Figure 2 Kaplan-Meier survival curves for clinical outcomes in the total population. (A) Major adverse cardiovascular events (MACE), (B) Stroke, (C) Myocardial infarction (MI), and (D) All-cause mortality.

Figure 3 Kaplan-Meier survival curves for clinical outcomes in propensity score-matched population. (A) Major adverse cardiovascular events (MACE), (B) Stroke, (C) Myocardial infarction (MI), and (D) All-cause mortality.

Figure 4 Results of subgroup analyses.

ACS, acute coronary syndrome; DHP-CCBs, dihydropyridine calcium channel blockers.

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Table 1 Baseline characteristics of the two groups before and after PSM

	Before PSM			After PSM	
Variables	Nicorandil and DHP-CCBs N = 1843	DHP-CCBs alone N = 5570	*P*-value	Nicorandil and DHP-CCBs N = 1315	DHP-CCBs alo N = 1315
Age, year, mean (SD)	64.9 (10.8)	65.0 (11.8)	0.623	64.0 (10.1)	64.1 (10.9
≤ 65 years, n (%)	959 (52.0)	2880 (51.7)		721 (54.8)	711 (54.1)
> 65 years, n (%)	884 (48.0)	2690 (48.3)	0.806	594 (45.2)	604 (45.9)
Male, n (%)	1188 (64.5)	3421 (61.4)	0.020	845 (64.3)	832 (63.3)
Smoking, n (%)	350 (22.7)	945 (20.2)	0.032	314 (23.9)	314 (23.9)
Revascularization*, n (%)	1081 (67.3)	3335 (65.4)	0.173	887 (67.5)	911 (69.3)
Comorbidities					
Diabetes, n (%)	709 (38.5)	2484 (44.6)	< 0.001	503 (38.3)	518 (39.4)
Hypertension, n (%)	1602 (87.0)	5203 (93.4)	< 0.001	1149 (87.4)	1180 (89.7
Hyperlipidemia, n (%)	291 (15.8)	1641 (30.5)	< 0.001	238 (18.1)	227 (17.3)
ACS, n (%)	829 (45.0)	1525 (27.4)	< 0.001	634 (48.2)	634 (48.2)
Stable angina, n (%)	131 (7.1)	711 (12.8)	< 0.001	84 (6.4)	90 (6.8)
Unstable angina, n (%)	618 (33.5)	1235 (22.2)	< 0.001	486 (37.0)	495 (37.6)
Heart failure, n (%)	47 (2.6)	116 (2.1)	0.235	40 (3.0)	30 (2.3)
In-hospital medications					

Antiplatelets, n (%)	1797 (97.5)	4737 (85.0)	< 0.001	1282 (97.5)	1292 (98.3
Nitrates, n (%)	1681 (91.2)	4523 (81.2)	< 0.001	1207 (91.8)	1207 (91.8
BBs	1612 (87.5)	4181 (75.1)	< 0.001	1152 (87.6)	1144 (87.0
ACEI/ARBs, n (%)	1518 (82.4)	3093 (55.5)	< 0.001	1106 (84.1)	1110 (84.4
Statins, n (%)	1818 (98.6)	5083 (91.3)	< 0.001	1297 (98.6)	1303 (99.1
MRAs, n (%)	540 (29.3)	1239 (22.2)	< 0.001	353 (26.8)	351 (26.7)

Notes: *including percutaneous coronary intervention and coronary artery bypass graft

ACEI/ARBs, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers; ACS, acute coronary syndrome; MR
beta-adrenergic receptor blockers; DHP-CCBs, dihydropyridine calcium channel blockers; MRA, mineralocorticoid receptor
propensity score matching

Table 2 IDRs of MACE, MI, stroke, and all-cause mortality of patients during follow-up

	Nicorandil and DHP-CCBs			DHP-CCBs alone		
	Events, n	P-Y	Incidence density (95% CI)	Events, n	P-Y	Incidence density (
MACE	221	1302.82	169.63 (148.68, 193.54)	235	1085.13	216.56 (190.57, 2
Stroke	121	1349.72	89.65 (75.02, 107.13)	179	1082.27	165.39 (142.86, 1
MI	113	1366.95	82.67 (68.75, 99.40)	81	1145.59	70.71 (56.87, 8
All-cause mortality	24	1369.76	17.52 (11.74, 26.14)	13	950.95	13.67 (7.94, 23

Notes: IDR, incidence density ratio; P-Y, person-years; DHP-CCBs, dihydropyridine calcium channel blockers; MACE, major
infarction; CI, confidence interval

Table 3 Sensitivity analyses

	HR (95%CI)	*P*-value	E-value	E-value 95% CI LL
PSM with trimming				
MACE	0.81 (0.67, 0.97)	0.0230	1.78	1.20
Stroke	0.56 (0.44, 0.70)	< 0.0001	2.99	2.20
MI	1.21 (0.91, 1.61)	0.1848	1.72	1.00
All-cause mortality	1.25 (0.63, 2.45)	0.5210	1.80	1.00
Limited to patients admitted after nicorandil been available in China				
MACE	0.78 (0.65, 0.94)	0.0076	1.89	1.34
Stroke	0.56 (0.44, 0.70)	< 0.0001	2.99	2.20
MI	1.11 (0.84, 1.47)	0.4677	1.46	1.00
All-cause mortality	1.09 (0.56, 2.12)	0.8035	1.40	1.00

Notes: CI, confidence interval; HR, hazard ratio; PSM, propensity score matching; LL, lower limit; MACE, major adverse cardiovascular events; MI, myocardial infarction