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RESEARCH ARTICLE

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

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Abstract

Objective: This study was aimed at investigating whether the addition of nicorandil to a dihydropyridine calcium channel blocker (DHP-CCB) regimen might decrease 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, 7413 eligible patients with CHD were divided into DHP-CCB plus nicorandil combination (n = 1843) and DHP-CCB (n = 5570) 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, compared with DHP-CCBs alone, was associated with a lower risk of MACE (HR: 0.80, 95% CI: 0.67–0.97). The combination group also had a lower 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 revealed more prominent benefits of the combined treatment on MACE in patients with than without diabetes.

Conclusions: The combination of nicorandil and DHP-CCBs may be more beneficial than DHP-CCBs alone in decreasing long-term risks of MACE and stroke 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 resulting from stenosis of the coronary artery lumen and leading to typical symptoms of angina [1, 2]. Antiplatelet

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agents, anti-anginal drugs, and statins are cornerstones of CHD treatment, whereas revascularization is indicated for acute coronary syndrome (ACS) [3–6]. Despite recent advances in diagnosis and treatment, CHD remains a major cause of cardiovascular morbidity and mortality worldwide [7, 8]. Patients with CHD are at elevated risk of long-term incidence of major adverse cardiovascular events (MACE), typically including myocardial infarction (MI), stroke, and mortality [9, 10].

Calcium channel blockers (CCBs) are commonly used to treat hypertension and angina [11, 12]. On the basis of their chemistry and pharmacodynamics, CCBs are classified into two categories: dihydropyridine (DHP) and non-DHP CCBs [13]. Both categories may be used to treat coronary spasms, whereas 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 the coronary and systemic vasculature, thereby improving coronary perfusion and decreasing blood pressure [6, 14]. However, despite these benefits, only several clinical trials have shown benefits of DHP-CCBs on cardiovascular outcomes in patients with stable CHD [15–18].

Nicorandil is a nitrate-moiety nicotinamide ester that is widely used to treat angina [19]. As an adenosine-sensitive potassium (K(ATP)) channel opener, its mechanism of action is distinct from those of CCBs [20]. 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 [21]. Beyond its demonstrated clinical efficacy in alleviating the symptoms of angina, nicorandil may decrease the risks of MACE and mortality in patients with CHD [22, 23]. Given the increasing prevalence of patients with CHD who take nicorandil and DHP-CCBs concurrently, determining the effects of combining nicorandil with DHP-CCBs on the long-term incidence of MACE in these patients 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 with DHP-CCBs alone on MACE incidence in patients with CHD.

Methods

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

Study Design and Participants

We conducted a real-world retrospective cohort study evaluating patients with CHD hospitalized at 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. The inclusion criteria included age of 18 years or older; hospitalization for CHD treatment; treatment with DHP-CCBs with or without nicorandil at discharge; and availability of more than two sets of admission records. The exclusion criteria were patients with asymptomatic myocardial ischemia; cardiovascular conditions other than CHD (e.g., dilated, hypertrophic, or restrictive cardiomyopathies; cardiac amyloidosis; and congenital heart disease); or histories of cardiac transplantation or valve surgery.

Data Extraction

The methods of data extraction were as previously reported in detail [24]. In brief, pre-trained researchers collected medical information according to a predefined data extraction table from the various electronic medical record (EMR) systems of the participating medical centers. The primary medical electronic systems included the EMR, providing demographic characteristics, hospital registration date, date of diagnosis, and surgical records; the healthcare information system (HIS), providing

medical administrative data; and the laboratory information system, providing laboratory findings. The following data were extracted for each patient: (1) demographic characteristics, including age, sex, smoking history, and history of revascularization (percutaneous coronary intervention and/or coronary artery bypass grafting); (2) comorbidities and past medical histories of conditions such as hypertension, diabetes mellitus, hyperlipidemia, angina (stable or unstable), MI, ACS, or 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 the rates of individual components of MACE at the 3-year follow-up.

Statistical Analyses

Continuous variables are summarized as the mean value and standard deviation (SD), and categorized variables are reported as frequencies and percentages. Intergroup differences were examined with a two-sample Student's t-test or Wilcoxon rank sum test, and the chi-squared test or Fisher's exact probability test. Rates of primary and secondary outcomes were analyzed with Kaplan-Meier survival curves and the log-rank test, and are presented as the hazard ratio (HR) with corresponding 95% confidence interval (CI). 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, was 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 were as reported previously [24]. 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 stability of the findings was assessed with sensitivity analyses restricted to patients admitted after nicorandil became available in China and using PSM trimming (trimming of the propensity score distribution below the 5th percentile and above the 95th percentile). To assess the influence of unmeasured confounding factors, we calculated E-values, as previously reported [25]. In addition, we conducted subgroup analyses of the association between combined therapy and MACE according to predefined variables, including age, sex, ACS diagnosis, and 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 in the HIS and EMR system, after which 130,301 patients were excluded for the reasons listed in Figure 1. A total of 7413 patients were included in the final analysis. Of these, 1843 patients were treated with both DHP-CCBs and nicorandil (combination group), whereas 5570 patients were treated with DHP-CCBs without nicorandil (DHP-CCB 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 to be current smokers (22.7% vs. 20.2%, $P = 0.032$), whereas the DHP-CCB group had 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%, $P < 0.001$). The mean age and prevalence rates of previous coronary revascularization and heart failure were similar between groups. After PSM for the entire population, the baseline characteristics were well

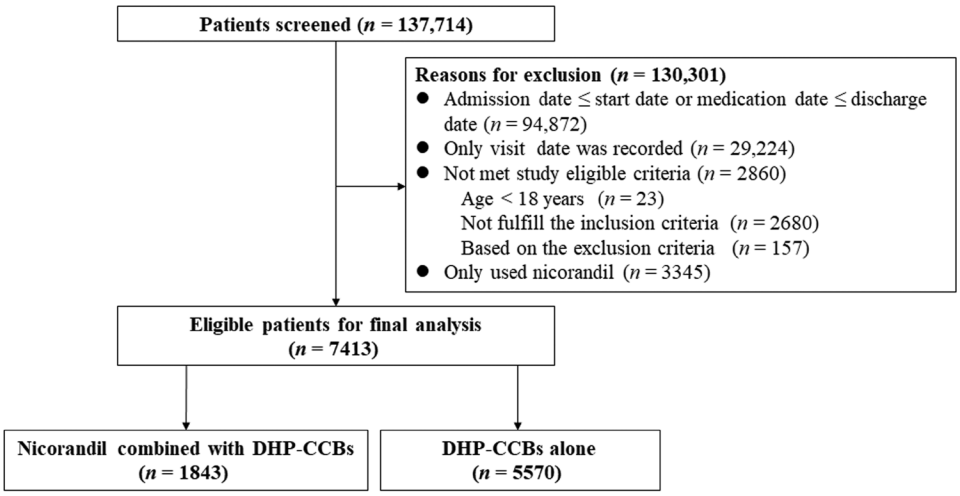

Figure 1 Flowchart of Patient Inclusion and Exclusion.
CHD, coronary heart disease; DHP-CCBs, dihydropyridine calcium channel blockers; EMR, electronic medical record; HIS, healthcare information system.

balanced between groups (all P > 0.05), and 1315 patients were included 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, at the 3-year follow-up, the combination group had significantly lower risks of MACE (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 with the DHP-CCB group, the combination group had lower incidence densities for MACE and stroke, whereas the incidence densities for 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, whereas 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

The 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 had a lower incidence of MACE and stroke than the DHP-CCB group (all P < 0.05). In addition, sensitivity analyses indicated similar incidence rates of MI and all-cause mortality between 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 indicated no significant interactions between demographic and clinical characteristics such as age, sex, ACS diagnosis, smoking status, hypertension, and hyperlipidemia on the benefits of nicorandil combined with DHP-CCBs in terms of MACE incidence (Figure 4, all P for subgroup interactions > 0.05). However, subgroup analysis suggested that comorbid diabetes might have significantly affected the effectiveness of the combined nicorandil and DHP-CCBs. The benefits of the combined treatment on MACE were more pronounced in patients with than without diabetes (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 7413 patients with CHD, and

Table 1 Baseline Characteristics of the Two Groups Before and After PSM.

Variables	Before PSM			After PSM			
	Nicorandil and DHP-CCBs N = 1843	DHP-CCBs alone N = 5570	P-value	Nicorandil and DHP-CCBs N = 1315	DHP-CCBs alone N = 1315	P-value	Weighted SD
Age, years, mean (SD)	64.9 (10.8)	65.0 (11.8)	0.623	64.0 (10.1)	64.1 (10.9)	0.708	0.005
≤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)	0.695	0.015
Male, n (%)	1188 (64.5)	3421 (61.4)	0.020	845 (64.3)	832 (63.3)	0.598	0.021
Smoking, n (%)	350 (22.7)	945 (20.2)	0.032	314 (23.9)	314 (23.9)	>0.999	0.00
Revascularization*, n (%)	1081 (67.3)	3335 (65.4)	0.173	887 (67.5)	911 (69.3)	0.314	0.039
Comorbidities							
Diabetes, n (%)	709 (38.5)	2484 (44.6)	<0.001	503 (38.3)	518 (39.4)	0.548	0.023
Hypertension, n (%)	1602 (87.0)	5203 (93.4)	<0.001	1149 (87.4)	1180 (89.7)	0.058	0.074
Hyperlipidemia, n (%)	291 (15.8)	1641 (30.5)	<0.001	238 (18.1)	227 (17.3)	0.574	0.022
ACS, n (%)	829 (45.0)	1525 (27.4)	<0.001	634 (48.2)	634 (48.2)	>0.999	0.00
Stable angina, n (%)	131 (7.1)	711 (12.8)	<0.001	84 (6.4)	90 (6.8)	0.638	0.018
Unstable angina, n (%)	618 (33.5)	1235 (22.2)	<0.001	486 (37.0)	495 (37.6)	0.717	0.014
Heart failure, n (%)	47 (2.6)	116 (2.1)	0.235	40 (3.0)	30 (2.3)	0.226	0.047
In-hospital medications							
Antiplatelets, n (%)	1797 (97.5)	4737 (85.0)	<0.001	1282 (97.5)	1292 (98.3)	0.177	0.053
Nitrates, n (%)	1681 (91.2)	4523 (81.2)	<0.001	1207 (91.8)	1207 (91.8)	>0.999	0.000
BBs	1612 (87.5)	4181 (75.1)	<0.001	1152 (87.6)	1144 (87.0)	0.639	0.018
ACEI/ARBs, n (%)	1518 (82.4)	3093 (55.5)	<0.001	1106 (84.1)	1110 (84.4)	0.830	0.008
Statins, n (%)	1818 (98.6)	5083 (91.3)	<0.001	1297 (98.6)	1303 (99.1)	0.271	0.043
MRAs, n (%)	540 (29.3)	1239 (22.2)	<0.001	353 (26.8)	351 (26.7)	0.930	0.003

Notes: *Including percutaneous coronary intervention and coronary artery bypass grafting.

ACEI/ARBs, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers; ACS, acute coronary syndrome; MRA, mineralocorticoid receptor antagonist; BBs, beta-adrenergic receptor blockers; DHP-CCBs, dihydropyridine calcium channel blockers; MRA, mineralocorticoid receptor antagonist; SD, standardized deviation; PSM, propensity score matching.

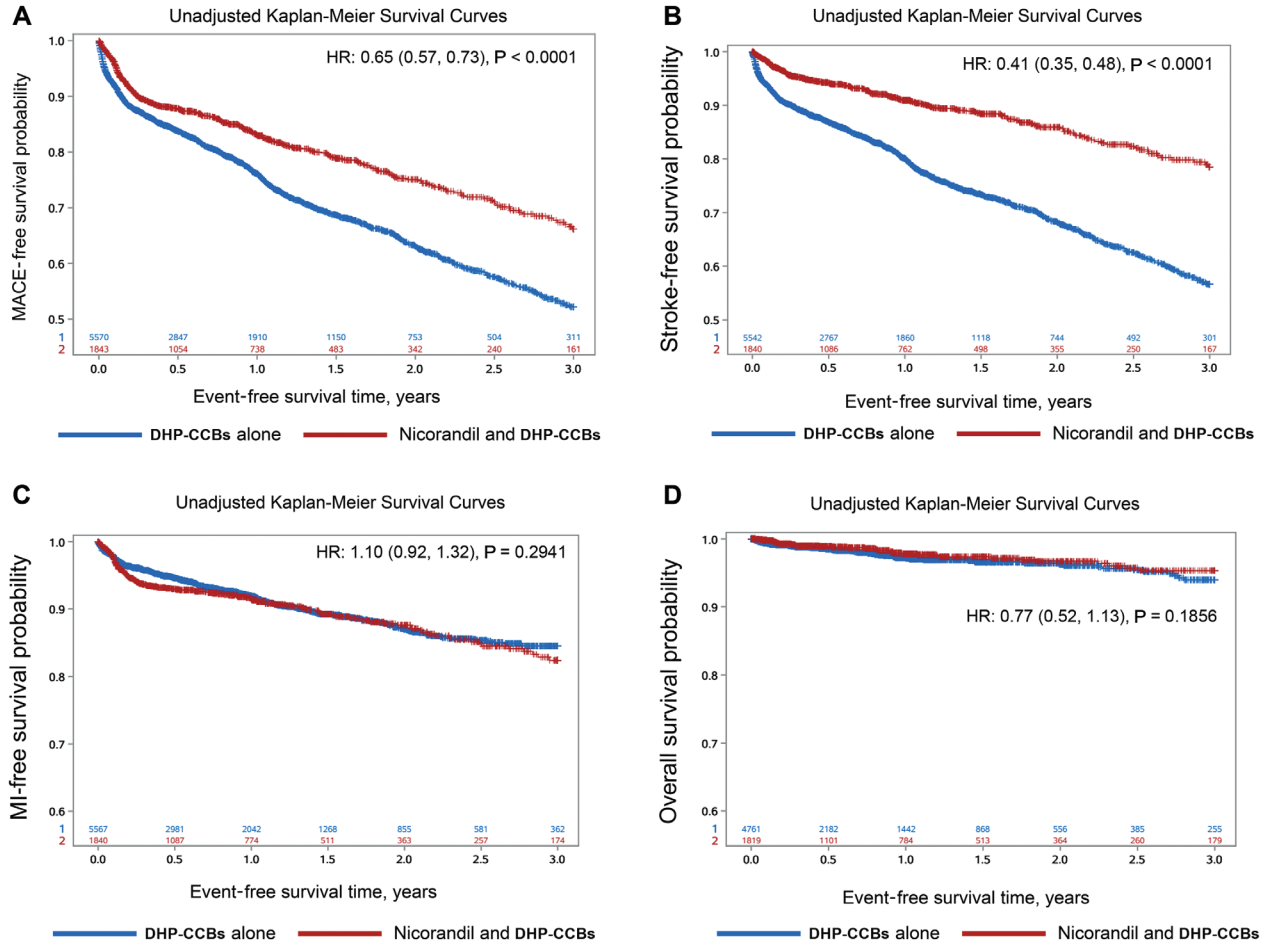

Figure 2 Kaplan-Meier Survival Curves for Clinical Outcomes in the Total Population.
(A) Major adverse cardiovascular events (MACE). (B) Stroke. (C) Myocardial infarction (MI). (D) All-cause mortality.

observed that combined treatment with nicorandil and DHP-CCBs, compared with DHP-CCBs alone, was associated with a significantly lower incidence of MACE during the 3-year follow-up. Subsequent analysis according to the components of MACE demonstrated that combined treatment was associated with a significantly lower risk of stroke, but not incidence of MI or all-cause mortality. These results persisted 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 subgroup analyses except for the subgroup analysis according to diabetes status, which showed a more pronounced benefit of combined treatment on MACE in patients with than without diabetes. Together, our findings suggested that the combination of nicorandil and DHP-CCBs might be more beneficial than DHP-CCBs alone in decreasing 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.

Our real-world observational study included all available patients with CHD who met the inclusion criteria without limitations of disease severity, thus enhancing the applicability of the results to daily clinical practice. DHP-CCBs dilate coronary arteries and may confer an additional benefits in the treatment of angina [26]. Moreover, in view of the contrasting pharmacodynamics and efficacies of DHP- and non-DHP CCBs, we included only patients treated with DHP-CCBs to minimize potential confounding variables. Although many patients with CHD, particularly those with hypertension, use DHP-CCBs, the effects on clinical outcomes have not been fully determined [26]. The Coronary disease Trial Investigating Outcome with

Table 2 IDRs of MACE, MI, Stroke, and All-cause Mortality of Patients During Follow-up.

	Nicorandil and DHP-CCBs			DHP-CCBs alone			IDR	
	Events, n	P-Y	Incidence density (95% CI)	Events, n	P-Y	Incidence density (95% CI)	Rate ratio (95% CI)	P
MACE	221	1302.82	169.63 (148.68, 193.54)	235	1085.13	216.56 (190.57, 246.10)	0.78 (0.65, 0.94)	0.0091
Stroke	121	1349.72	89.65 (75.02, 107.13)	179	1082.27	165.39 (142.86, 191.49)	0.54 (0.43, 0.68)	<0.0001
MI	113	1366.95	82.67 (68.75, 99.40)	81	1145.59	70.71 (56.87, 87.91)	1.17 (0.88, 1.56)	0.2831
All-cause mortality	24	1369.76	17.52 (11.74, 26.14)	13	950.95	13.67 (7.94, 23.54)	1.28 (0.65, 2.52)	0.4711

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

Nifedipine (ACTION) trial has demonstrated that long-acting nifedipine decreases the incidence of coronary angiography and cardiovascular interventions in stable CHD, but does not improve MACE-free survival [17]. Similarly, nifedipine, compared with atenolol, has not been found to improve the composite outcome of cardiac death, nonfatal MI, and unstable angina in the Total Ischaemic Burden European Trial (TIBET) [27]. 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, and may ameliorate the symptoms of patients with CHD, particularly those with microvascular dysfunction [4]. Increasing evidence indicates the potential benefits of nicorandil on cardiovascular outcomes. In the landmark Impact of Nicorandil in Angina (IONA) trial, nicorandil, compared with placebo, has been found to significantly decrease the incidence of MACE in patients with CHD with concomitant use of anti-anginal agents including CCBs [28]. In the subsequent Japanese Coronary Artery Disease (JCAD) study, nicorandil has been found to result in lower all-cause mortality than observed in a propensity-matched control group of patients with stable angina [29]. 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 to be synergistic [30]. However, few studies have evaluated the efficacy of nicorandil in decreasing stroke risk in patients with CHD. Our study showed that, compared with DHP-CCBs, combined treatment with nicorandil and DHP-CCBs was associated with a significantly lower incidence of MACE and the component event of stroke in patients with CHD. A rat model study has demonstrated that during subacute ischemic stroke, nicorandil improves neurobehavioral and motor function, and decreases the sizes of ischemic lesions [31]. Moreover, preclinical studies have suggested a neuroprotective role of nicorandil through attenuation of neuroinflammation during cerebral ischemic injury [32–34]. Further studies are needed to validate our findings and to determine the molecular mechanisms underlying the benefits of nicorandil on stroke.

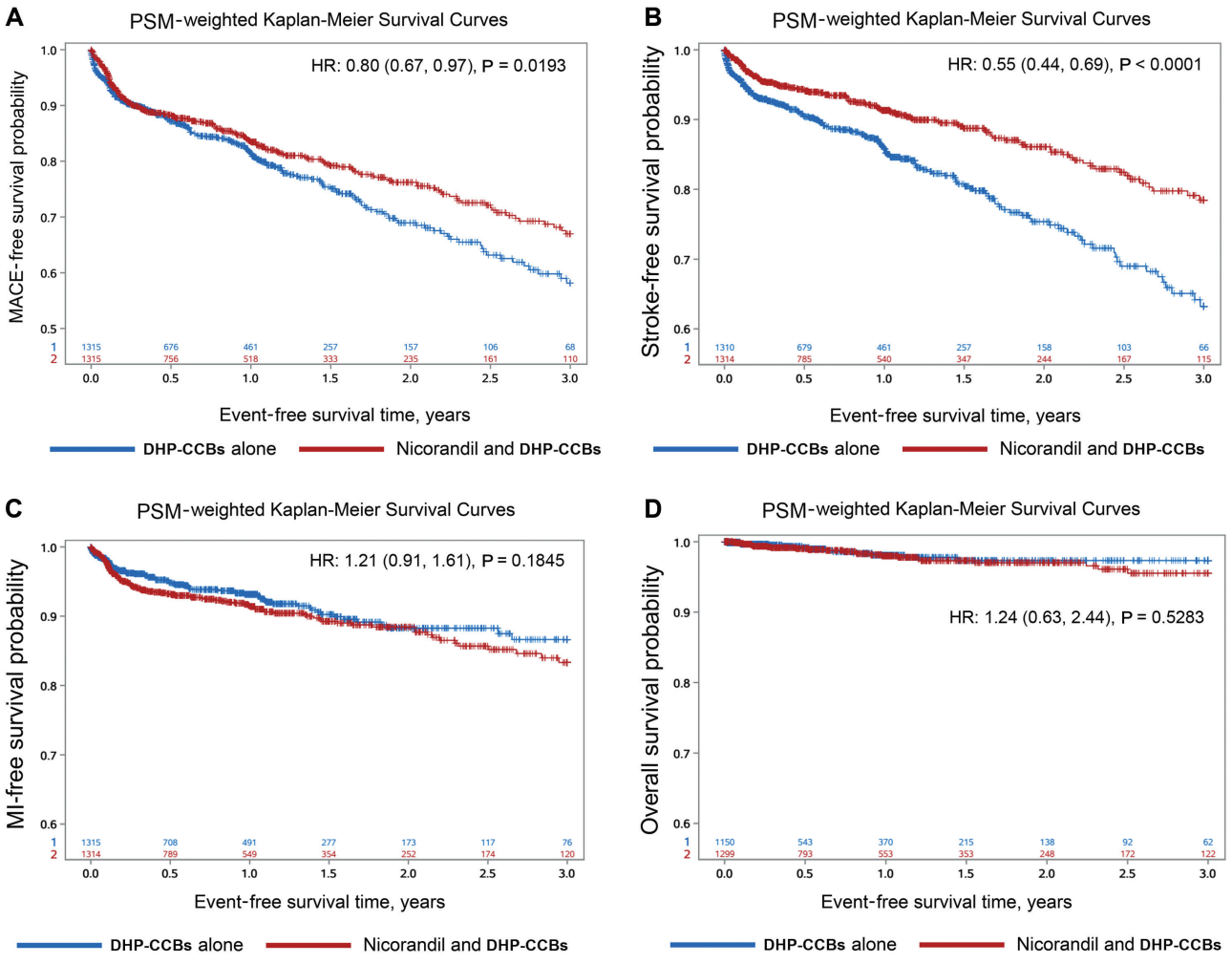

Figure 3 Kaplan-Meier Survival Curves for Clinical Outcomes in a Propensity Score-matched Population.
(A) Major adverse cardiovascular events (MACE). (B) Stroke. (C) Myocardial infarction (MI). (D) All-cause mortality.

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 became 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.

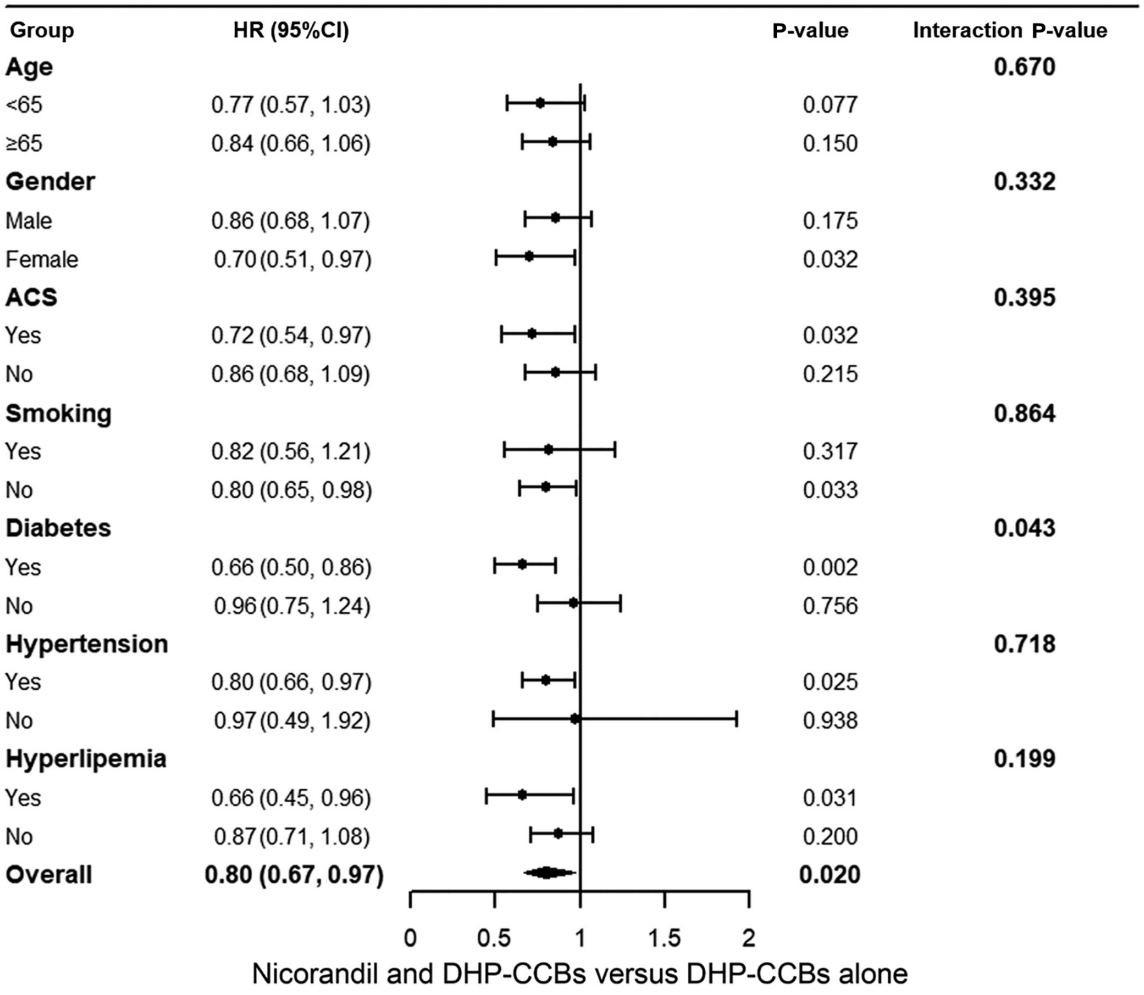

Figure 4 Results of Subgroup Analyses.
ACS, acute coronary syndrome; DHP-CCBs, dihydropyridine calcium channel blockers.

In this study, subgroup analysis showed that the benefit of the combined treatment on MACE might be more pronounced in patients with than without diabetes. 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 [35, 36]. Prospective clinical studies should be considered to validate the potential benefits of nicorandil in patients with diabetes and CHD.

This study has several limitations. First, because of its observational design, the study could not establish a causal relationship between combined treatment and decreased incidence of MACE and stroke. However, our findings strongly support the value of a prospective clinical trial for further validation. A second limitation was the retrospective study design. Although we screened consecutive patients with CHD from two medical centers for eligibility, recall and selection biases may have confounded the results. Third, because 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 were not included; thus, we were unable to evaluate the effects of these drugs on such patients in this study. Therefore future studies should be considered to further investigate this aspect. 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 therefore necessary to evaluate the efficacy of nicorandil-non-DHP CCB combinations. In addition, although we applied PSM analysis to minimize the influence of potential confounding factors on the outcomes, potential unidentified factors were not adjusted for and might have affected the results. For example, the prevalence of atrial fibrillation might affect the risk of stroke and therefore have confounded the results. However, we were unable to determine the influence of atrial fibrillation, 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 might have been missed in a real-world context, because of the use of alternative diagnostic codes. Finally, the follow-up duration was limited to 3 years. Prospective studies with longer follow-up durations should be performed to validate the long-term effectiveness of the combined treatment in patients with CHD.

Conclusions

Nicorandil combined with DHP-CCBs may be more effective than DHP-CCBs alone in decreasing 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.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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).

Author Contributions

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

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Conflict of Interest

The authors have no conflicts of interest to declare.

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