Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Nicorandil Use and Health Status Outcomes in Patients with Angina Pectoris: A Prospective, Multicenter, Cohort Study (GREAT)

Xiliang Zhao[1], Guojie Cheng[2], Liling Sun[3], Yajuan Liu[4], Xin Du[1], Su'e Xu[5], Litao Wu[6], Ying Wei[7], Wei Liu[8], Lifu Miao[9], Qihua Zhang[4], Changsheng Ma[1], Yong Zeng[1]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Department of Cardiology, Beijing Daxing District People's Hospital, Beijing, People's Republic of China; [3]Department of Cardiology, Beijing Changping District Hospital, Beijing, People's Republic of China; [4]Department of Cardiology, Beijing Miyun District Hospital, Peking University First Hospital, Beijing, People's Republic of China; [5]Department of Cardiology, Huai'an Hospital of Traditional Chinese Medicine, Jiangsu, People's Republic of China; [6]Department of Cardiology, Ruyang People's Hospital, Henan, People's Republic of China; [7]Rehabilitation Medicine Center, Qilu Hospital of Shandong University, Dezhou Hospital, Shandong, People's Republic of China; [8]Department of Cardiology, Beijing Jishuitan Hospital, Capital Medical University, The Fourth Clinical Medical College of Peking University, Beijing, People's Republic of China; [9]Heart Center, First Affiliated Hospital of Tsinghua University, Beijing, People's Republic of China

Correspondence: Yong Zeng, Department of Cardiology, Beijing Anzhen Hospital, Beijing, 100029, People's Republic of China, Tel +86 13501373114, Email yzeng_anzhen@mail.ccmu.edu.cn

Purpose: Coronary artery disease represents a major clinical burden, and angina pectoris is the most frequent manifestation of coronary artery disease. Nicorandil is commonly used for the management of angina pectoris; however, its effects on health status outcomes are unclear.

Patients and Methods: This multicenter, prospective, cohort study (GREAT) enrolled 1556 adult coronary artery disease patients with angina pectoris from nine hospitals in China. Patients were classified into nicorandil and control groups. The primary outcome was the change in the Seattle Angina Questionnaire summary score (SAQ-SS) from baseline to 12 months. Secondary outcomes included changes in SAQ-SS at 3, 6, and 9 months. Propensity score matching (PSM) was used to reduce bias and control for confounding factors.

Results: We analyzed 1528 patients with baseline and 12-month health status data. After PSM, 450 matched pairs of patients were identified. A difference of ≥5 points for SAQ-SS is considered clinically significant. Patients in the nicorandil group reported greater mean improvement in SAQ-SS (17.6 ± 14.0, difference: 2.50, 95% CI: 0.74–4.27; P=0.003) at 12 months compared with the control group (15.1 ± 13.0; *P*=0.003). Similar trends were noted in SAQ-SS at 3, 6, and 9 months. Additionally, nicorandil users exhibited significantly greater improvements in the SAQ physical limitation (11.7 ± 16.9 vs 8.4 ± 16.9; difference: 3.27, 95% CI, 1.05–5.48; P =0.001) and SAQ-QoL domain (18.9 ± 21.4 vs 16.3 ± 20.4; difference: 2.62, 95% CI, −0.12 to 5.35; P=0.042) at 12 months. Most patients in the entire cohort (78.4%) reported a clinical improvement in SAQ-SS. The nicorandil group had a higher proportion of patients with at least large improvements (≥20 points) in SAQ-SS (42.5% vs 32.9%; difference: 9.7%, 95% CI: 3.3–16.0; P= 0.004).

Conclusion: Among patients with angina pectoris, anti-angina treatment improved the majority of patients' health status. Nicorandil-based regimens were associated with a greater health status outcome improvement compared to those not using nicorandil in coronary artery disease patients with angina pectoris. A substantial proportion of patients using nicorandil exhibited noteworthy improvements in health status outcomes at one year.

Registration: ClinicalTrials.gov, NCT05050773.

Keywords: angina pectoris, real-world, nicorandil, coronary artery disease, health-related outcomes, Seattle angina questionnaire

Introduction

Cardiovascular disease is estimated to affect around 330 million people and accounts for two out of every five deaths in China, ranking first in causes of death for urban and rural residents.[1,2] Angina pectoris, a common manifestation of coronary artery disease, exerts a considerable impact on mortality and reduces patients' quality of life.[3–7] Management of

Received: 28 November 2024
Accepted: 23 August 2025
Published: 15 September 2025

angina pectoris generally includes preventive therapies to reduce cardiovascular events risk and medication therapies to control symptoms but there is an unmet need for prospective and standardized monitoring to ensure timely treatment.[8]

The Seattle Angina Questionnaire (SAQ), developed by Spertus in 1994, is a self-assessment tool for evaluating functional status and quality of life in patients with coronary heart disease.[9] In 2003, a Chinese version of the SAQ was validated, demonstrating its reliability and ease of use, with 93.7% of respondents finding it easy to complete.[10] With the expansion of digital tools, the assessment of patient reported outcomes by using electronic equipment (e-PRO) is becoming a promising and economically viable approach, as real-time health status monitoring allows early detection of patients at risk.

There is no clear differentiation of the available anti-anginal regimens; a meta-analysis of anti-anginal therapies showed they all exert similar efficacy for reducing angina symptoms.[11] Given the lack of evidence demonstrating superiority of any one anti-anginal drug over another, the treatment of angina pectoris symptoms varies between different countries and is usually at the discretion of the healthcare provider. Nicorandil (Chugai Pharmaceutical Co. Ltd, Tokyo, Japan) is an adenosine triphosphate-sensitive potassium channel (K_{ATP}) activator used for angina pectoris therapy that has been shown to improve clinical outcomes, relieve angina, and reduce the incidence of cardiovascular events in patients with ischemic heart disease.[12–17] Multiple clinical trials have demonstrated the efficacy and safety of nicorandil-based regimens in patients with angina pectoris.[18–20]

Although nicorandil therapy has been recommended as an add-on therapy to β-blockers and calcium channel blockers in patients whose symptoms are not controlled, or as monotherapy for properly selected patients,[21–23] the use of nicorandil to predict health status benefits in patients with angina pectoris has not been described. To address this gap in knowledge, we analyzed patients enrolled in a multicenter, prospective cohort registry study (GREAT) to assess the effect of nicorandil on health status outcomes over 1 year.

Methods

Study Design and Patients

This multicenter, prospective, cohort study (GREAT) was conducted across nine hospitals in China. A detailed description of the study design has been published previously and is summarized here in brief.[24] Patients with coronary artery disease who had angina pectoris were recruited through continuous and competitive enrolment among study sites between September 2021 and May 2022. Patients were eligible if they had a diagnosis of angina pectoris (AP) confirmed by coronary angiography or CTA within the past year, showing ≥50% stenosis with angina symptoms, or <50% stenosis with symptoms plus a positive treadmill test, stress echo, or radionuclide stress test. Post-PCI stenosis of the left vessels had to be ≤50%. Patients also needed to be using or deemed suitable for at least one oral anti-anginal drug (eg, β-blockers, nitrates, calcium antagonists, or potassium channel openers), possess basic literacy skills, be able to complete the SAQ after training, use a smartphone, and provide informed consent. Patients were excluded if they had malignant tumors with a life expectancy under one year, had joined another clinical study within the past month, or were considered unsuitable due to poor compliance or other conditions. Eligibility also required the ability to continue or initiate oral anti-anginal therapy and accurately complete the SAQ after instruction. Enrolled patients were observed for 12 months after enrolment. Remote follow-up visits occurred at 3-, 6- and 9-months' observation. A final follow-up visit occurred on site at 12 months.

This study was conducted in full accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice. All study documents and procedures were approved by the Ethics Committee (EC)/Institutional Review Board of the leading study site, Beijing Anzhen Hospital (EC 2021-KLS-07), and of all participating sites prior to the start of the study, in accordance with local laws, regulations, and the requirements of relevant organizations. Written, informed consent was obtained from each patient before study participation. The study was registered at ClinicalTrials.gov (NCT05050773).

Data Collection

Demographics, angina regimens (eg β-blockers, calcium channel blockers, nicorandil, and nitrates), medical and medication history, comorbidities, angina pectoris severity as per the Canadian Cardiovascular Society (CCS) classification of angina and Rose angina questionnaire, were recorded during the baseline visit.[25–27] All enrolled patients were

registered in the study-specific ePRO system hosted on a novel WeChat Mini program platform and provided with a user account. Once registered, patients could answer questionnaires and upload imaging from any unexpected clinic visits.

During the remote follow-up visits (3, 6, and 9 months), SAQ scores were collected via the WeChat Mini program platform on a mobile phone, or telephone call follow-up visit, along with reports of anti-anginal medication use, medication adjustments, and frequency of angina attacks in the prior 4 weeks. Any additional examination data were also collected through the ePRO system via optical character recognition technology. During the final follow-up visit (at 12 months), medication information, radiographic and other additional examination, frequency of angina attacks, SAQ scores and adverse events were recorded.

Control of Bias

To minimize potential selection, information, and confounding biases, a series of specific measures were undertaken, which are described in the Supplementary Materials.

Health Status Outcomes and SAQ Summary Score

Primary outcome was the change in SAQ summary score (SAQ-SS) at 12-month from baseline. Secondary outcomes were the changes in SAQ-SS at 3, 6, and 9 months from baseline. The SAQ is a 19-item questionnaire comprising five domains: anginal frequency (SAQ-AF), anginal stability (SAQ-AS), physical limitation (SAQ-PL), quality-of-life (SAQ-QoL), and treatment satisfaction (SAQ-TS).[28] Responses in each domain are scored, and an average of the AF, PL, and QoL domain scores provides the SAQ-SS. All SAQ scores range from 0 to 100, with higher scores indicating less frequent angina, fewer physical limitations, and better QoL/higher levels of functioning. This study used a Chinese version of the SAQ that has been shown to be a valid and reliable instrument.[29,30] SAQ-SS can be categorized into four levels: 0–24 (from very poor to poor health), 25–49 (poor to fair), 50–74 (fair to good), and 75–100 (good to excellent).[31] A difference of ≥5 points for SAQ-SS is considered clinically significant.[31] Change in SAQ-SS was stratified as had at least clinical benefit (≥5 points), had at least intermediate improvement (≥10 points), had at least large improvement (≥20 points), and had at least very large improvement (≥30 points).

Statistical Analyses

The sample size calculation was reported in the study protocol article.[24] In a prior follow-up study involving patients with AP, the enhancement in SAQ-SS after 12 months of therapy was roughly,[18] irrespective of the medication used.[32] Consequently, a sample size of 1245 patients, as determined by sampling survey techniques, was required to attain a comparable SAQ-SS with a margin of error of 1 and a significance level of $\alpha = 0.05$. Furthermore, factoring in a 20% dropout rate, the study aimed to recruit a minimum of 1556 patients with AP. In brief, 1556 patients with angina pectoris were included in the study. Statistical analyses were performed using SAS (Statistical Analysis Software 9.4, SAS Institute Inc, Cary, North Carolina, USA). Descriptive statistics were used to report categorical variables; continuous variables were summarized as means, standard deviation, median, minimum and maximum values. The full analysis set (FAS) comprised all patients who had at least one follow-up recorded of SAQ post-enrolment. The safety set (SS) was used for adverse events collection.

Primary and secondary outcomes were evaluated based on the FAS. A Wilcoxon rank-sum test, Fisher's exact test, or Chi-square test, as appropriate, was used to compare baseline characteristics and outcomes between treatment groups.

The PSM method was used to correct for data bias and confounding factors. Propensity scores were calculated for each patient by conducting a multivariate logical regression analysis on 31 variables; the list of included matching variables can be found in Supplementary Table 1. A combination of neighbor and caliper matching was used with a 1:1 ratio to match individuals in the nicorandil and control groups with the closest propensity scores. The caliper width for matching was set at 0.25. For missing data, a propensity score was generated for each observation to estimate the probability that the observation was missing. These observations were then grouped based on the propensity scores and an approximate Bayesian bootstrap imputation was applied to each group.[33,34] After matching, the standardized biases were all less than 0.2, indicating a balanced matching outcome. Treatment effect was compared in different subgroup populations using a Wilcoxon rank-sum test.

Medication adherence was evaluated using the proportion of days covered, defined as the ratio of actual medication treatment days to the total follow-up days. Adherence data were based on the overall days of baseline anti-anginal treatment, not specific medications. A proportion of days covered greater than 80% indicated good adherence. The monotonic trend effect of daily nicorandil dosage on the percentage of relative baseline change in SAQ-SS was evaluated using the permutation-based Jonckheere-Terpstra test, while the correlation between daily nicorandil dosage and the percentage of relative baseline change in SAQ-SS was analyzed via Spearman correlation analysis. To assess the robustness of our main findings, we implemented a range of statistical adjustment methods based on the framework proposed by Keele and Grieve.[35]

Results

Baseline Characteristics

A total of 1575 patients were screened, of whom 1556 were registered from nine hospitals, 19 were excluded because they did not meet the inclusion criteria. Finally, 1528 patients who completed the study were analyzed. Patients were classified into two groups, among whom 529 (34.6%) used nicorandil (nicorandil group) and 999 (65.4%) not use nicorandil (control group). The patient flow diagram is presented in Figure 1.

The baseline characteristics, and medication information of the two groups before and after PSM is presented in Table 1. Before PSM, patients in the nicorandil group were more likely to be non-drinkers, have unstable angina, have undergone percutaneous coronary intervention, have a family history of coronary artery disease, and have hypertension compared with the control group.

Following PSM, 450 matched pairs of patients were identified, and relevant variables were leveraged to generate propensity scores (Supplementary Figure 1). Baseline characteristics for the two groups were well balanced (Table 1); in the nicorandil and control groups, the median age was 60 years and 61 years, respectively, most patients were male (74.2% and 73.3%, respectively), had a body mass index (BMI) ≥24.0 kg/m^2 (76.9% and 72.2%, respectively), had received percutaneous coronary intervention (71.3% and 68.9%, respectively), and had CCS angina severity grade 1 (70.7% and 67.1%, respectively). Approximately half of patients had never smoked (48.2% and 47.6%, respectively) and

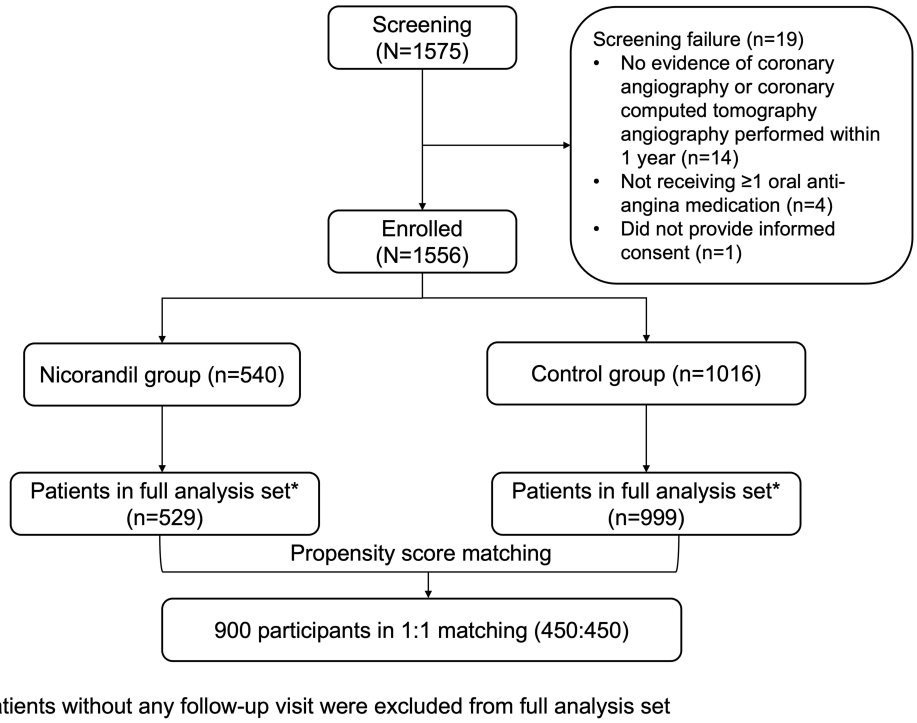

Figure 1 Patient Flow Diagram. *Patients without any follow-up visit were excluded from full analysis set.

Table 1 Demographics, Baseline Characteristics and Anti-Angina Treatments in Patients Pre- and Post-PSM

Characteristics	*Pre-PSM*			*Post-PSM*		
	Nicorandil (n=529)	**Control group (n=999)**	***P* value**	**Nicorandil (n=450)**	**Control group (n=450)**	***P* value**
Median age, years (Q1, Q3)	60 (53–67)	61 (54–68)	0.201[a]	60 (53–67)	61 (53–68)	0.374[c]
Sex, n (%)			0.063[b]			0.762[b]
Male	394 (74.5)	699 (70.0)		334 (74.2)	330 (73.3)	
Female	135 (25.5)	300 (30.0)		116 (25.8)	120 (26.7)	
BMI, n (%)			0.336[a]			0.333[a]
18.5–<24.0 kg/m^2	119 (22.5)	260 (26.1)		101 (22.4)	119 (26.4)	
24.0–<28.0 kg/m^2	264 (49.9)	477 (47.9)		223 (49.6)	216 (48.0)	
≥28.0 kg/m^2	142 (26.8)	246 (24.7)		123 (27.3)	109 (24.2)	
Smoking, n (%)			0.330[c]			0.795[c]
Never smoked	263 (49.7)	474 (47.5)		218 (48.4)	215 (47.8)	
Smoker	153 (29.0)	332 (33.3)		131 (29.1)	143 (31.7)	
Former smoker, quit smoking	113 (21.4)	192 (19.2)		101 (22.4)	92 (20.4)	
Alcohol consumption, n (%)			<0.001[b]			0.646[b]
Non-drinker	443 (83.7)	783 (78.5)		371 (82.4)	370 (82.2)	
Current drinker	56 (10.6)	178 (17.8)		54 (12.0)	60 (13.3)	
Former drinker	30 (5.7)	37 (3.7)		25 (5.6)	20 (4.4)	
Angina type, n (%)			<0.001[b]			0.911[b]
Stable angina	35 (6.6)	130 (13.0)		34 (7.6)	38 (8.4)	
Unstable angina	406 (76.8)	696 (69.8)		333 (74.0)	324 (72.0)	
Post-myocardial infarction angina	83 (15.7)	138 (13.8)		78 (17.3)	82 (18.2)	
Duration of coronary heart disease, n (%)			0.811[a]			0.973[a]
<5 years	423 (80.1)	756 (79.3)		357 (79.3)	358 (79.6)	
5–10 years	53 (10.0)	93 (9.8)		45 (10.0)	46 (10.2)	
>10 years	52 (9.9)	104 (10.9)		48 (10.7)	46 (10.2)	
Surgical interventions for coronary heart disease, n (%)			<0.001[c]			0.547[c]
PCI	382 (72.2)	602 (60.4)		321 (71.3)	310 (68.9)	
CABG	9 (1.7)	11 (1.1)		8 (1.8)	6 (1.3)	
Family history of coronary heart disease, n (%)	109 (20.6)	197 (19.7)	<0.001[b]	94 (20.9)	89 (19.8)	0.849[b]
Diabetes, n (%)	195 (36.9)	378 (37.8)	0.714[c]	171 (38.0)	172 (38.2)	>0.999[c]
Hypertension, n (%)	398 (75.2)	668 (66.9)	<0.001[b]	336 (74.7)	326 (72.4)	0.683[b]
Dyslipidemia, n (%)	356 (67.3)	691 (69.2)	0.690[c]	305 (67.8)	301 (66.9)	0.873[c]
Chronic kidney disease, n (%)	7 (1.3)	23 (2.3)	0.010[c]	6 (1.3)	9 (2.0)	0.199[c]
Gout, n (%)	2 (0.4)	12 (1.2)	0.002[c]	2 (0.4)	3 (0.7)	0.217[c]
COPD, n (%)	4 (0.8)	13 (1.3)	0.090[c]	4 (0.9)	3 (0.7)	>0.999[c]

(*Continued*)

https://doi.org/10.2147/DDDT.S506108

https://doi.org/10.2147/DDDT.S506108

Table 1 (Continued).

Characteristics	*Pre-PSM*			*Post-PSM*		
	Nicorandil (n=529)	**Control group (n=999)**	***P* value**	**Nicorandil (n=450)**	**Control group (n=450)**	***P* value**
Heart failure, n (%)	9 (1.7)	31 (3.1)	0.068[c]	9 (2.0)	11 (2.4)	0.822[c]
Cerebrovascular disease, n (%)			0.053[c]			0.351[c]
Stroke	9 (1.7)	35 (3.5)		8 (1.8)	16 (3.6)	
TIA	2 (0.4)	9 (0.9)		2 (0.4)	3 (0.7)	
Arrhythmias, n (%)			0.646[c]			0.586[c]
Atrial fibrillations	9 (1.7)	25 (2.5)		9 (2.0)	13 (2.9)	
Other cardiac conditions, n (%)			0.005[c]			0.686[c]
Left ventricular hypertrophy	3 (0.6)	11 (1.1)		3 (0.7)	1 (0.2)	
Heart valve disorders	2 (0.4)	5 (0.5)		2 (0.4)	3 (0.7)	
CCS angina severity grading, n (%)			<0.001[a]			0.593[a]
I	394 (74.5)	595 (59.6)		318 (70.7)	302 (67.1)	
II	85 (16.1)	324 (32.4)		84 (18.7)	99 (22.0)	
III	22 (4.2)	40 (4.0)		20 (4.4)	18 (4.0)	
IV	28 (5.3)	40 (4.0)		28 (6.2)	31 (6.9)	
Coronary artery stenosis grading (coronary angiography), n (%)			<0.001[a]			0.749[a]
II	1 (0.2)	1 (0.1)		1 (0.2)	1 (0.2)	
III	59 (11.2)	167 (16.7)		54 (12.0)	63 (14.0)	
IV	276 (52.2)	568 (56.9)		240 (53.3)	236 (52.4)	
V	78 (14.7)	120 (12.0)		63 (14.0)	70 (15.6)	
VI	114 (21.6)	142 (14.2)		92 (20.4)	80 (17.8)	
Rose angina questionnaire, n (%)	259 (49.0)	486 (48.7)	0.980[b]	229 (50.9)	241 (53.6)	0.507[b]
Medications at baseline, n (%)						
Lipid-lowering agents	526 (99.4)	966 (97.3)	0.004[b]	447 (99.3)	444 (98.7)	0.506[b]
β-blockers	344 (65.0)	720 (72.5)	0.002[b]	309 (68.7)	316 (70.2)	0.612[b]
Drugs acting on the renin-angiotensin system	286 (54.1)	550 (55.4)	0.621[c]	250 (55.6)	240 (53.3)	0.503[b]
Nitrates	269 (50.9)	611 (61.5)	<0.001[b]	243 (54.0)	247 (54.9)	0.789[b]
Calcium channel blockers	193 (36.5)	362 (36.5)	0.991[b]	167 (37.1)	171 (38.0)	0.783[b]
Chinese medicine for angina pectoris	160 (30.3)	144 (14.5)	<0.001[b]	111 (24.7)	94 (20.9)	0.177[b]

Notes: [a]Wilcoxon rank-sum test; [b]Chi-square test; [c]Fisher's exact test.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; PSM, propensity score matching; TIA, transient ischemic attack.

around one third had diabetes (38.0% and 38.2%, respectively). More than half of patients in both groups had a positive Rose angina questionnaire (50.9% and 53.6%, respectively). Almost all patients used lipid-lowering agents (99.3% vs 98.7%), and around 70% used β-blockers (68.7% vs 70.2%) in both groups, respectively.

Follow up and Medication Adherence

The 12-month follow-up rate was 93.8%. After PSM, medication adherence results showed that 84.0% of patients in the nicorandil group and 86.4% in the control group had proportion of days covered ≥80% at 12 months. The difference between the two groups was not statistically significant (P=0.124). Overall proportion of days covered results at 3, 6, 9, and 12 months are presented in Supplementary Table 2.

Health Status Outcomes

At baseline, the majority of patients in both groups (62.4% vs 68.4%; P <0.001) had SAQ-SS in the 50–74 range; at 12 months, most of patients in both groups (71.1% vs 74.2%; P =0.27) had improved their SAQ-SS to the 75–100 range. Sankey diagram depicts the change of SAQ-SS from baseline to each follow up visit post-PSM (Figure 2). For instance, in the nicorandil group, 12.9% of patients with baseline scores in 25–49 range improved to 75–100 range at the 3-month of follow-up, and 8.7% of the patients improved to 50–74 range. Additionally, 34.2% of patients in the 50–75 range improved to scores in the 75–100 range. In comparison, the corresponding proportions in the control group were 4.2%, 6.0%, and 42.0%, respectively. Distribution of patients within SAQ-SS score range at each follow-up visit is provided in Supplementary Table 3.

Table 2 provides a comparison of SAQ scores at baseline and 12 month, and 12-month changes between the two groups post-PSM. SAQ-SS were significantly lower in the nicorandil group compared to the control group at baseline (P<0.001), this difference was no longer significant at 12 months (P=0.088). The changes in SAQ-SS at 12 months was significantly greater in the nicorandil group compared to the control group (17.6 ± 14.0 vs 15.1 ± 13.0, difference: 2.50, 95% CI: 0.74–4.27; P=0.003). Sensitivity analysis shows the consistent trend with the above result (Supplementary Table 4). Further, we observed that the differences were mainly contributed by SAQ-PL domain (11.7 ± 16.9 vs 8.4 ± 16.9; difference: 3.27, 95% CI: 1.05–5.48; P =0.001) and SAQ-QoL domain (18.9 ± 21.4 vs 16.3 ± 20.4; difference: 2.62, 95% CI: −0.12 to 5.35; P=0.042) in the nicorandil group compared to the control group.

The secondary outcomes, changes in SAQ-SS at 3, 6, and 9 months, are detailed in Table 3. The nicorandil group exhibited significantly greater improvements in SAQ-SS compared to the control group at each follow-up visit (P < 0.05 for each visit). The SAQ subdomain changes at 3, 6, and 9 months are also provided in Table 3.

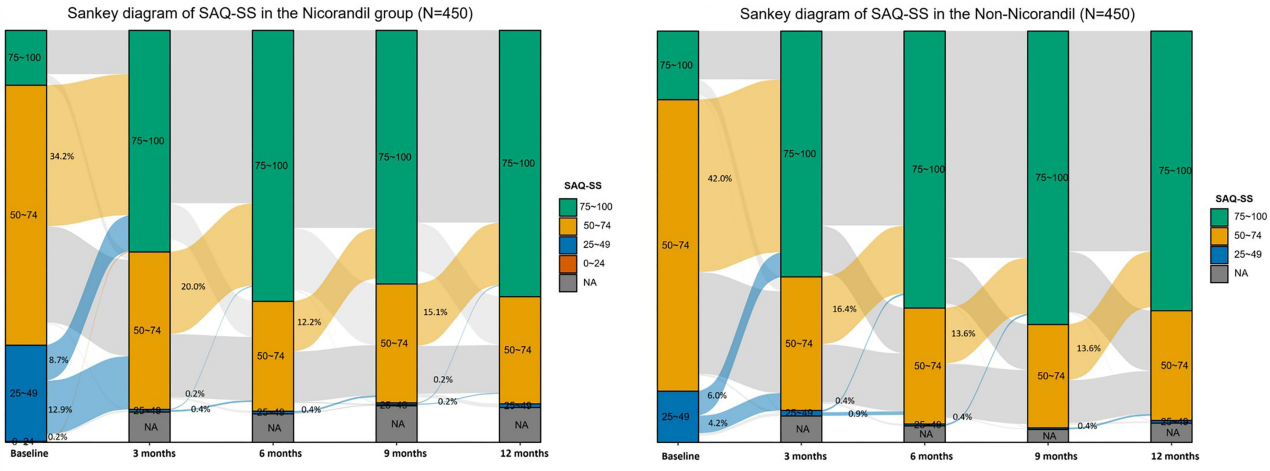

Figure 2 SAQ-SS Changes from Baseline to 12 Months Display with Sankey Flow Diagrams (post-PSM). SAQ-SS categories were defined as: 0–24 (from very poor to poor health), 25–49 (poor to fair), 50–74 (fair to good), and 75–100 (good to excellent).
Abbreviation: SAQ-SS, Seattle Angina Questionnaire summary score.

https://doi.org/10.2147/DDDT.S506108

https://doi.org/10.2147/DDDT.S506108

Table 2 SAQ Scores and Changes at 12 months (Post-PSM)

	SAQ Scores at Baseline			SAQ scores at 12 Months			Changes at 12 Months		
	Nicorandil (n=450)	**Control Group (n=450)**	***P* value**	**Nicorandil (n=450)**	**Control Group (n=450)**	***P* value**	**Nicorandil (n=450)**	**Control Group (n=450)**	***P* value**
SAQ-SS[a]	59.1± 13.4	62.7± 2.2	<0.001	76.7 ± 8.2	77.7 ± 7.0	0.088	17.6 ± 14.0	15.1 ± 13.0	0.003
SAQ-AF	71.2± 21.7	74.3± 9.2	0.062	93.3± 13.8	94.8 ± 10.7	0.585	22.1 ± 24.1	20.5 ± 20.9	0.293
SAQ-QoL	40.4± 19.8	44.4± 8.9	0.005	59.2± 12.7	60.6 ± 13.8	0.153	18.9 ± 21.4	16.3 ± 20.4	0.042
SAQ-PL	65.8± 15.4	69.3± 4.6	<0.001	69.9 ± 9.9	70.6 ± 9.9	0.207	11.7 ± 16.9	8.4 ± 16.9	0.001

Notes: [a] Data were missing for one patient. All P-values calculated using the Wilcoxon rank-sum test.

Table 3 Changes in SAQ Scores at 3, 6, and 9 Months (Post-PSM)

Change from Baseline	Nicorandil (n=450)	Control group (n=450)	*P* value[a]
SAQ-SS			
3 months	15.3 ± 13.4	13.0 ± 13.8	0.032
6 months	17.8 ± 14.0	14.8 ± 12.6	0.001
9 months	17.2 ± 14.0	15.2 ± 13.1	0.015
SAQ-AF			
3 months	19.0 ± 23.7	17.0 ± 22.3	0.227
6 months	20.8 ± 23.4	18.1 ± 21.1	0.162
9 months	21.7 ± 22.8	20.1 ± 19.7	0.298
SAQ-QoL			
3 months	22.7 ± 21.7	21.0 ± 21.1	0.497
6 months	25.1 ± 21.4	20.8 ± 21.4	0.031
9 months	22.2 ± 22.7	19.6 ± 21.9	0.084
SAQ-PL			
3 months	4.2 ± 15.9	1.1 ± 15.9	0.003
6 months	7.4 ± 17.0	5.4 ± 15.7	0.069
9 months	7.6 ± 16.8	6.0 ± 16.8	0.113

Notes: [a]Wilcoxon rank-sum test. Data are mean ± standard deviation.
Abbreviations: PSM, propensity score matching; SAQ, Seattle Angina Questionnaire; SAQ-AF, SAQ-anginal frequency; SAQ-PL, SAQ-physical limitation; SAQ-QoL, SAQ-quality of life; SAQ-SS, SAQ-summary score.

To clarify the clinical benefit of SAQ improvement, we analyzed the changes in SAQ-SS in non-exclusive categories (Table 4). The results showed that most patients (78.4%) reported a clinical improvement in SAQ-SS (≥5 points) in the entire cohort post-PSM, with a slightly higher proportion of improvement in the nicorandil group versus the control group (79.7% vs 77.1%; $P = 0.339$). A significantly higher proportion of nicorandil-treated patients had an at least intermediate improvement (≥10 points: 71.3% vs 62.7%; difference: 8.6%, 95% CI: 2.5–14.7; P =0.008), an at least large improvement (≥20 points: 42.5% vs 32.9%; difference: 9.7%, 95% CI:3.3–16.0; P =0.004), and at least very large improvement (≥30 points: 18.5% vs 12.2%; difference: 6.3%, 95% CI:1.6–11.0; P =0.012) compared with the control group.

Subgroup Analysis

A subgroup analysis of mean change in SAQ-SS from baseline to 12 months found significantly greater improvements with the nicorandil versus the control group in patients aged <65 years, without diabetes, with controlled hypertension, and in male patients (Figure 3).

Table 4 Proportion of Patients in SAQ-SS Changes Non-Exclusive Categories From Baseline to 12 Months (Post-PSM)

	Nicorandil (n=449)[a]	Control group (n=450)	*P* value[b]
At least minimal (≥5)	358 (79.7)	347 (77.1)	0.339
At least intermediate (≥10)	320 (71.3)	282 (62.7)	0.006
At least large (≥20)	190 (42.5)	147 (32.9)	0.007
At least very large (≥30)	82 (18.2)	54 (12.0)	0.020

Notes: [a]Data were missing for one patient; [b]Chi-square test. Data are reported as n (%).
Abbreviations: PSM, propensity score matching; SAQ-SS, Seattle Angina Questionnaire summary score.

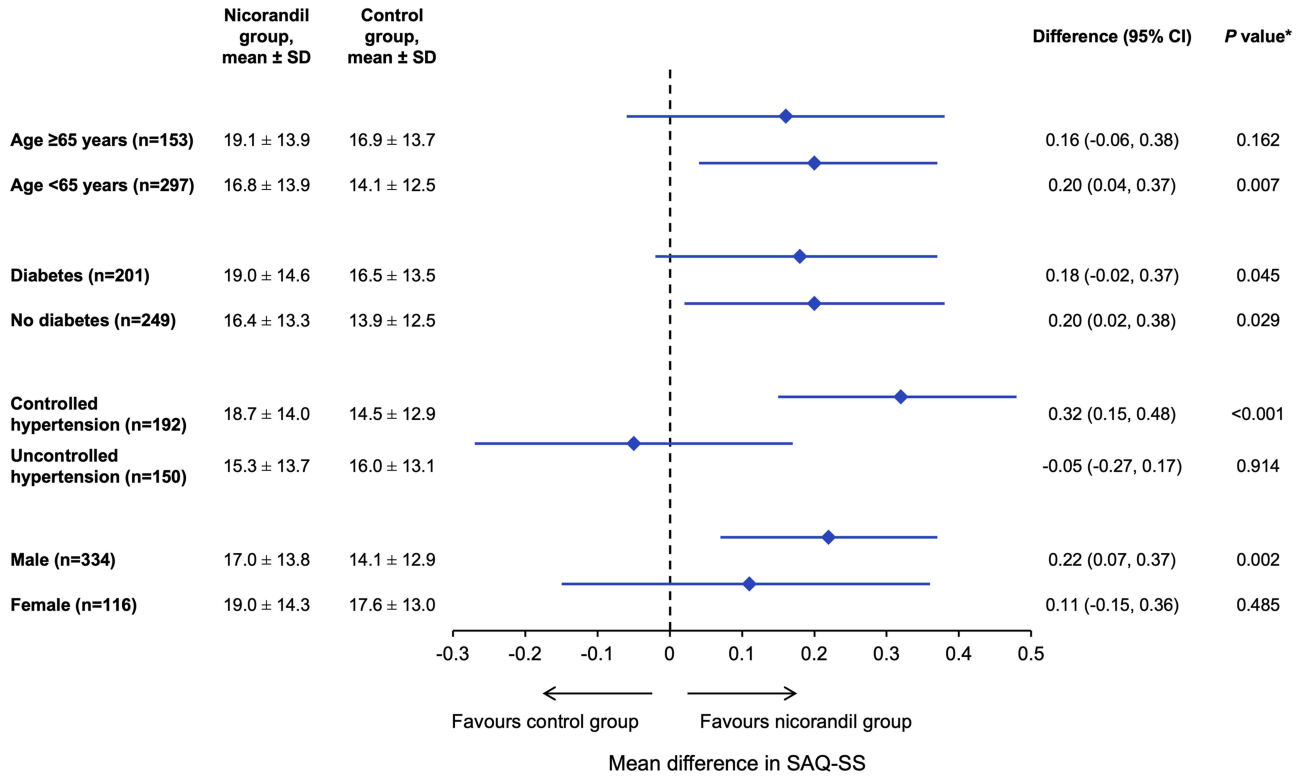

Figure 3 Subgroup Analysis of Mean SAQ-SS Change from Baseline to 12 Months. *Wilcoxon rank-sum test.
Abbreviations: CI, confidence interval; SAQ-SS, Seattle Angina Questionnaire summary score; SD, standard deviation.

Other Clinical Outcomes

In the SS population, during the study period, the number of deaths was three in the nicorandil group and five in the control group. Myocardial infarction (MI) occurred only once, exclusively in the control group. No rehospitalizations occurred in the nicorandil group, whereas three cases were reported in the control group.

Dose-Response Analysis

To ensure consistent medication duration among patients, dropout cases in the nicorandil group were excluded, and 486 patients who completed all follow-up visits were enrolled for the exploratory dose-response analysis. Patients were categorized into three groups based on daily nicorandil dosage: ≤10 mg (n=4), 15 mg (n=477), and 30 mg (n=5).

Findings showed that the 30 mg group had the highest median percentage of relative baseline change in SAQ-SS scores (36.1%), followed by the 15 mg group (30.0%) and the ≤10 mg group (5.0%). Statistically, no significant difference was observed among the three groups (P=0.24). Further analysis revealed no significant correlation between daily nicorandil dosage and relative baseline change in SAQ-SS scores (correlation coefficient r=0.07, P=0.10). Additionally, no significant monotonic trend effect of SAQ-SS relative baseline change with increasing dosage was detected (P=0.09) (Supplementary Figure 2).

Discussion

In this multicenter, prospective, registry-based cohort study assessing health status outcomes of patients with coronary artery disease in real-world settings, we found that patients receiving nicorandil-based regimens reported significantly greater improvements in SAQ-SS from baseline to 12 months (P =0.003) compared with those on control group regimens. Improvements were also significantly greater in the SAQ-QoL (P =0.042) and SAQ-PL (P =0.001) domains. Notably, although patients in the nicorandil group had a lower mean baseline SAQ-SS, a greater proportion (42.5% and 18.2%, respectively) had at least large or very large improvements in SAQ-SS at 12 months.

Clinical trial data comparing the efficacy of anti-anginal agents are limited and a systematic review of the available evidence showed no advantage for one anti-anginal agent over another.[11] A recent small randomized clinical trial involving 60 patients with stable angina pectoris demonstrated that nicorandil significantly improved SAQ scores compared with conventional treatment.[36] In our study of over 500 participants using nicorandil, most of whom were followed up for 12 months, findings indicate that nicorandil-based anti-anginal regimens provide greater health status benefits compared to control group-based regimens in patients with angina pectoris in routine clinical practice.

An important finding of this study is that a high proportion of patients in the nicorandil group demonstrated significant health status improvements at 12 months. The magnitude of improvement was consistently greater in the nicorandil group, suggesting that patients with angina pectoris may stand to benefit from using nicorandil treatment. In fact, over 70% of patient in the nicorandil group reported at least intermediate improvement in SAQ-SS. Furthermore, subgroup analysis results from the present study suggest the benefits of receiving nicorandil-based regimens may be greatest in younger (<65 years of age), non-diabetic male patients with controlled hypertension. Older age, diabetes and hypertension are all known risk factors for coronary artery disease in patients with angina pectoris.[22] Therefore, these results may reflect nicorandil exerting a greater benefit in patient groups at lower risk of coronary artery disease. A sensitivity analysis is shown in Supplementary Table 4. However, male sex is associated with a higher risk of coronary artery disease in patients presenting with angina pectoris.[22] Clinically, nicorandil is commonly used for the treatment of microvascular angina.[37]

Interestingly, while all patients included in this study had diagnosed angina pectoris at enrolment, only half reported as positive on the Rose angina questionnaire. The Rose angina questionnaire is widely used as a standardized method for assessing angina in population-based health surveys in Western populations.[27] The Rose questionnaire has acceptable sensitivity and specificity for identifying angina. The sensitivity ranges from 29.9% to 50.7%, and the specificity ranges from 91.6% to 95.0%. Its positive predictive value is around 42.7% to 42.8%. The questionnaire's performance is not significantly affected by age or social class.[26] However, since the Rose angina questionnaire was developed in English, cultural differences must be considered when translating and using this questionnaire in non-English-speaking populations.[38] A previous study in older adults in China reported that the prevalence of doctor-diagnosed angina pectoris was greater than that according to the Rose angina questionnaire. Moreover, patient educational level and socioeconomic factors influenced the reporting of chest pain and the translation of the Rose angina questionnaire, with doctor-diagnosed angina pectoris and Rose angina questionnaire angina pectoris showing a better association in urban, higher occupational class, or higher educational level populations.[39] Taken together, these findings suggest that the Rose angina questionnaire should be used in combination with healthcare provider assessments in China.

Currently, the SAQ measures are widely accepted as tools to quantify symptomatic responses to therapy in clinical research. One potential advantage of this study is the application of an ePRO system embedded in a mobile phone. This ePRO system was integrated into the WeChat Mini program platform, which is widely used in mainland China. This integration makes it convenient for participants, especially elderly patients, to report angina symptoms during remote follow-up periods. Additionally, it enables timely monitoring of angina pectoris, helping to reduce the risk of cardiovascular events by better detecting underestimated angina symptoms. Utilizing the ePRO system and SAQ measurements to predict health outcomes and benefits for coronary artery disease patients with angina pectoris in daily practice presents an intriguing avenue for future research. Future studies could explore health status outcomes of other different anti-angina regimens or focus on patients with a history of revascularization to provide insights into angina management in clinical settings.

The limitations of the present study have previously been described in detail.[24] In addition, there were several other potential limitations that should be considered. Firstly, during PSM, the baseline SAQ score was not included as a matching variable. Therefore, while the baseline characteristics of the two groups were well balanced for other key variables after PSM, baseline SAQ scores were worse in the nicorandil group compared with the control group. This reflects clinical practice, as nicorandil is a second-line treatment for angina pectoris and is generally given to patients with poor health status and low SAQ scores at baseline. Nonetheless, in our study, patients receiving nicorandil-based regimens had greater improvements in SAQ-SS, SAQ-QoL, and SAQ-PL scores at 12 months, despite being in poorer health at the beginning of the study. Secondly, medication adherence is a limitation due to the observational nature of the study. We assessed adherence by evaluating the proportion of days on anti-anginal medication compared with the total follow-up days and found no significant difference between the two groups. This finding excluded the possibility that

differences in health status outcomes were due to variations in real-world medication adherence. Finally, procedural outcomes (major adverse cardiac events, complete revascularization) were not systematically collected in this study. Over 70% of patients in this study had undergone surgical interventions, and it is unknown whether the procedural outcomes differed based only on the anti-anginal regimens received. Future studies are needed to further determine clinical outcomes based on anti-anginal regimens, to help identify best practices post-procedure.

Conclusion

In conclusion, we found that anti-angina treatment improved the majority of patients' health status. Nicorandil-based anti-angina regimens are associated with a greater health status outcome improvement compared to those not using nicorandil in coronary artery disease patients with angina pectoris. A substantial proportion of patients using nicorandil exhibited noteworthy improvements in health status outcomes at one year.

Abbreviations

BMI, body mass index; CCS, Canadian Cardiovascular Society; FAS, full analysis set; K_{ATP}, potassium channel; PSM, propensity score matching; SAQ, Seattle Angina Questionnaire; SAQ-AF, SAQ anginal frequency; SAQ-AS, SAQ anginal stability; SAQ-PL, SAQ physical limitation; SAQ-QoL, SAQ quality-of-life; SAQ-SS, SAQ summary score; SAQ-TS, SAQ treatment satisfaction.

Data Sharing Statement

The data supporting the results reported in this study are available from the corresponding author on reasonable request.

Acknowledgments

The authors would like to acknowledge and thank Chugai Pharma China Co., Ltd for providing funding for medical writing assistance. Jake Burrell, PhD (Rude Health Consulting Ltd.) provided editorial support for this paper.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Beijing Life Oasis Public Service Center.

Disclosure

The authors have no competing interests to declare that are relevant to the content of this article.

References

1. The Writing Committee Of The Report On Cardiovascular Health And Diseases In China. Report on cardiovascular health and diseases in China 2022: an updated summary. *Biomed Environ Sci*. 2023;36(8):669–701. doi:10.3967/bes2023.106
2. Zhou M, Wang H, Zhu J, et al. Cause-specific mortality for 240 causes in China during 1990–2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. *Lancet*. 2016;387(10015):251–272. doi:10.1016/s0140-6736(15)00551-6
3. Gandjour A, Lauterbach KW. Review of quality-of-life evaluations in patients with angina pectoris. *Pharmacoeconomics*. 1999;16(2):141–152. doi:10.2165/00019053-199916020-00003
4. Jespersen L, Abildstrøm SZ, Hvelplund A, Prescott E. Persistent angina: highly prevalent and associated with long-term anxiety, depression, low physical functioning, and quality of life in stable angina pectoris. *Clin Res Cardiol*. 2013;102(8):571–581. doi:10.1007/s00392-013-0568-z
5. Pocock SJ, Henderson RA, Seed P, Treasure T, Hampton JR. Quality of life, employment status, and anginal symptoms after coronary angioplasty or bypass surgery. 3-year follow-up in the Randomized Intervention Treatment of Angina (RITA) Trial. *Circulation*. 1996;94(2):135–142. doi:10.1161/01.cir.94.2.135
6. Rehman S, Rehman E, Mumtaz A, Jianglin Z. Cardiovascular disease mortality and potential risk factor in China: a multi-dimensional assessment by a grey relational approach. *Int J Public Health*. 2022;67:1604599. doi:10.3389/ijph.2022.1604599

7. Wu J, Han Y, Xu J, et al. Chronic stable angina is associated with lower health-related quality of life: evidence from Chinese patients. *PLoS One*. 2014;9(5):e97294. doi:10.1371/journal.pone.0097294
8. Ohman EM. Clinical practice. chronic stable angina. *N Engl J Med*. 2016;374(12):1167–1176. doi:10.1056/NEJMcp1502240
9. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle angina questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25(2):333–341. doi:10.1016/0735-1097(94)00397-9
10. Liu SH. *Reliability, Validity and Responsiveness of Chinese Version of Seattle Angina Questionnaire (SAQ)*. Tianjin Medical University; 2003. doi:10.7666/d.y524578
11. Ferrari R, Pavasini R, Camici PG, et al. Anti-anginal drugs-beliefs and evidence: systematic review covering 50 years of medical treatment. *Eur Heart J*. 2019;40(2):190–194. doi:10.1093/eurheartj/ehy504
12. Group IS. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet*. 2002;359(9314):1269–1275. doi:10.1016/s0140-6736(02)08265-x
13. Luo B, Wu P, Bu T, Zeng Z, Lu D. All-cause mortality and cardiovascular events with nicorandil in patients with IHD: systematic review and meta-analysis of the literature. *Int J Cardiol*. 2014;176(3):661–669. doi:10.1016/j.ijcard.2014.07.007
14. Okamura A, Rakugi H, Ohishi M, et al. Additive effects of nicorandil on coronary blood flow during continuous administration of nitroglycerin. *J Am Coll Cardiol*. 2001;37(3):719–725. doi:10.1016/s0735-1097(00)01171-2
15. Secco GG, Parisi R, Mirabella F, et al. Old and new drugs for treatment of stable angina: new anti-anginal drugs and coronary revascularization. *Cardiovasc Hematol Agents Med Chem*. 2015;13(1):21–24. doi:10.2174/1871525713666141219114240
16. Wu M, Huang Z, Xie H, Zhou Z. Nicorandil in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis. *PLoS One*. 2013;8(10):e78231. doi:10.1371/journal.pone.0078231
17. Zhao F, Chaugai S, Chen P, Wang Y, Wang DW. Effect of nicorandil in patients with heart failure: a systematic review and meta-analysis. *Cardiovasc Ther*. 2014;32(6):283–296. doi:10.1111/1755-5922.12097
18. Jiang J, Li Y, Zhou Y, et al. Oral nicorandil reduces ischemic attacks in patients with stable angina: a prospective, multicenter, open-label, randomized, controlled study. *Int J Cardiol*. 2016;224:183–187. doi:10.1016/j.ijcard.2016.08.305
19. Zhang J, Xin Z. Metoprolol combined with nicorandil on unstable angina pectoris can reduce incidence of cardiovascular events and inflammatory reactions. *Am J Transl Res*. 2021;13(7):7906–7913.
20. Zhu WL, Shan YD, Guo JX, et al. Double-blind, multicenter, active-controlled, randomized clinical trial to assess the safety and efficacy of orally administered nicorandil in patients with stable angina pectoris in China. *Circ J Jun*. 2007;71(6):826–833. doi:10.1253/circj.71.826
21. National Institute for Health and Care Excellence. Stable angina: management; 2016. Available from: https://www.nice.org.uk/guidance/cg126/. Accessed October, 2023.
22. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407–477. doi:10.1093/eurheartj/ehz425
23. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45:3415–3537. doi:10.1093/eurheartj/ehae177
24. Zhao X, Tong Z, Sun L, et al. Clinical characteristics, treatment patterns, and effectiveness in Chinese patients with angina pectoris using electronic patient-reported outcomes: protocol for a multicenter, prospective, cohort study (GREAT). *Adv Ther*. 2023;40(4):1899–1912. doi:10.1007/s12325-023-02425-0
25. Campeau L. Letter: grading of angina pectoris. *Circulation*. 1976;54(3):522–523. doi:10.1161/circ.54.3.947585
26. Lawlor DA, Adamson J, Ebrahim S. Performance of the WHO Rose angina questionnaire in post-menopausal women: are all of the questions necessary? *J Epidemiol Community Health*. 2003;57(7):538–541. doi:10.1136/jech.57.7.538
27. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ*. 1962;27(6):645–658.
28. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle angina questionnaire as an outcome measure in clinical trials and clinical care: a review. *JAMA Cardiol*. 2021;6(5):593–599. doi:10.1001/jamacardio.2020.7478
29. Liu X, Kong S, Liao Z, Sike L. Assessment study on physical function and the quality of life for CHD patients with SAQ. *Chin Behav Sci*. 1997;6:49–51.
30. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. *Circ Cardiovasc Qual Outcomes*. 2014;7(5):640–647. doi:10.1161/circoutcomes.114.000967
31. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med*. 2020;382(15):1408–1419. doi:10.1056/NEJMoa1916370
32. Saraste A, Knuuti J. ESC-Leitlinien 2019 fur die Diagnose und Therapie von chronischen Koronarsyndromen: empfehlungen fur die kardiovaskulare Bildgebung [ESC 2019 guidelines for the diagnosis and management of chronic coronary syndromes: recommendations for cardiovascular imaging]. *Herz*. 2020;45(5):409–420. doi:10.1007/s00059-020-04935-x
33. Lavori PW, Dawson R, Shera D. A multiple imputation strategy for clinical trials with truncation of patient data. *Stat Med*. 1995;14(17):1913–1925. doi:10.1002/sim.4780141707
34. Harel O, Zhou XH Multiple imputation: review of theory, implementation and software. *stat Med*. 2007;26(16):3057–3077. PMID: 17256804. doi:10.1002/sim.2787IF:1.8Q1
35. Keele L, Grieve R. So many choices: a guide to selecting among methods to adjust for observed confounders. *Stat Med*. 2025;44(5):e10336. doi:10.1002/sim.10336
36. Wang X, Chen H. Efficacy and safety of nicorandil in the treatment of stable angina pectoris. *Altern Ther Health Med*. 2024.
37. Jia Q, Shi S, Yuan G, et al. The effect of nicorandil in patients with cardiac syndrome X: a meta-analysis of randomized controlled trials. *Medicine*. 2020;99(37):e22167. doi:10.1097/md.0000000000022167
38. Hanna LC, Hunt SM, Bhopal RS. Using the Rose angina questionnaire cross-culturally: the importance of consulting lay people when translating epidemiological questionnaires. *Ethn Health*. 2012;17(3):241–251. doi:10.1080/13557858.2011.610439
39. Greaves K, Chen Y, Appadurai V, Hu Z, Schofield P, Chen R. The prevalence of doctor-diagnosed angina in 4314 older adults in China and comparison with the Rose angina questionnaire: the 4 province study. *Int J Cardiol*. 2014;177(2):627–628. doi:10.1016/j.ijcard.2014.09.126