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Association between Chinese herbal medicine and the composite outcome of repeat revascularization and in-stent restenosis in patients with chronic coronary syndrome undergoing percutaneous coronary intervention: a prospective cohort study

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ABSTRACT

OBJECTIVE To evaluate the association between adjunctive Chinese herbal medicine (CHM) and post-percutaneous coronary intervention (PCI) adverse cardiovascular events in patients with chronic coronary syndrome (CCS), and to identify subgroups that may derive greater benefit from integrative therapy.

METHODS This study included 2274 patients with CCS after PCI: 1155 patients in the guideline-directed medical treatment (GDMT) group and 1119 patients in the integrative Chinese and Western medicine (ICWM) group. Exposure was defined as cumulative CHM treatment for > 6 months per year. The primary endpoint was a composite of repeat revascularization and in-stent restenosis (ISR). Kaplan-Meier survival analysis and multivariable Cox regression models were used to assess associations between treatment strategy and study outcomes.

RESULTS A total of 1054 patients experienced the primary endpoint, including 575 patients (49.80%) in the GDMT group and 479 patients (42.80%) in the ICWM group. Compared with the GDMT group, the ICWM group had lower cumulative incidences of the primary endpoint, repeat revascularization, and ISR (log-rank $P < 0.001$, $P = 0.0018$, and $P = 0.023$, respectively). After full adjustment, ICWM was associated with lower risks of the primary endpoint (adjusted HR = 0.741, 95% CI: 0.654–0.841, $P < 0.001$), repeat revascularization (adjusted HR = 0.781, 95% CI: 0.686–0.889, $P < 0.001$), and ISR (adjusted HR = 0.825, 95% CI: 0.686–0.993, $P = 0.042$). Subgroup analyses suggested a more pronounced association in patients with prior PCI (adjusted HR = 0.59, 95% CI: 0.48–0.73, $P < 0.001$) and those without multivessel coronary artery disease (adjusted HR = 0.46, 95% CI: 0.32–0.68, $P < 0.001$).

CONCLUSIONS In this prospective cohort study, adjunctive CHM was associated with lower risks of the composite endpoint of repeat revascularization and ISR, as well as its individual components, in patients with CCS after PCI. The observed association appeared more pronounced in patients with prior PCI and those without multivessel coronary artery disease.

Coronary artery disease (CAD) remains the leading cause of mortality worldwide.[1] In China, an estimated 11.39 million individuals are affected by CAD, imposing a substantial economic burden and representing a major public health challenge.[2] When clinically stable, CAD is recognized as a chronic and progressive condition. Formerly termed "stable CAD", it has been reclassified in recent European Society of Cardiology guidelines as "chronic coronary syndrome (CCS)", a term that better reflects the dynamic clinical manifestations associated with CAD.[3,4] Despite recent therapeutic advances, this chronic disorder continues to be associated with substantial morbidity and mortality rates.[5] Percutaneous coronary intervention (PCI) is a major treatment strategy for patients with CCS. In China, the annual number of PCI procedures continues to increase, with 1.421 million patients undergoing PCI in 2022, accounting for 23.2% of all hospitalizations for CAD.[6] Although PCI achieves coronary flow reconstruction, it fails to mitigate residual risks associated with CCS, such as persistent chronic inflammation, endothelial dysfunction, and subs-

equent lesion progression. Even with standardized use of aspirin, clopidogrel, and statins after PCI, a considerable proportion of patients still develop in-stent restenosis (ISR) during long-term follow-up and ultimately undergo repeat revascularization.[7,8] In addition, some patients are unable to tolerate guideline-directed medical treatment (GDMT) due to adverse effects. Therefore, optimizing long-term pharmacological strategies to reduce the incidence of repeat revascularization and ISR remains an important clinical goal in the management of CCS after PCI.

Traditional Chinese medicine (TCM), characterized by overall concept of organic wholeness and treatment based on pattern differentiation, has shown potential value in the long-term management of CCS. Previous clinical studies have suggested that, compared with GDMT alone, integrative Chinese and Western medicine (ICWM) may improve angina-related symptoms in patients with CAD after PCI, reduce the risk of post-PCI adverse cardiovascular events, and contribute to better long-term outcomes.[9-12] These findings suggest that ICWM may help address some of the persistent challenges in the long-term management of CAD after PCI.

Because this study focused on CCS patients undergoing PCI, repeat revascularization and ISR were prespecified as the primary outcome, as they directly reflect lesion-related residual risk after PCI. By contrast, hard endpoints such as death, myocardial infarction (MI), or stroke are less frequent in clinically stable CCS and may be influenced by factors beyond the target lesion. Given the limited evidence regarding the role of Chinese herbal medicine (CHM) in improving outcomes among CCS patients after PCI, and the lack of clarity regarding which subgroups may derive greater benefit from ICWM therapy, this prospective cohort study aimed to evaluate the association between ICWM therapy and the risks of repeat revascularization and ISR in CCS patients after PCI. We also sought to identify subgroups that may derive greater benefit from this integrative strategy, thereby providing clinical evidence for the long-term management of CCS.

METHODS

Study Design and Participants

This study population was based on a large, prospective observational cohort. The original cohort consecutively recruited CAD patients who were hospitalized and received PCI at Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China from September 2016 to August 2017, enrolling a total of 5453 cases. This study has been registered at Chinese Clinical Trial Registry platform (https://www.chictr.org.cn/, trial registration number: ChiCTR1800017128) and was approved by the Ethics Review Committee of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (No.2016-786). It was conducted in strict compliance with the Declaration of Helsinki, and informed consent was obtained from each patient.

In the present study, based on the above, patients with CCS aged ≥ 18 years who underwent drug-eluting stent (DES) implantation were enrolled. Exclusion criteria were as follows: (1) patients with a definitive diagnosis of acute coronary syndrome at baseline; (2) patients with previous/proposed coronary artery bypass grafting at baseline; (3) patients with hypertriglyceridemia [triglycerides (TG) ≥ 500 mg/dL];[13-15] (4) patients with an incomplete baseline history; (5) patients with co-morbid multisystemic malignant disease; (6) patients with no results of coronary computed tomography angiography (CCTA) or coronary angiography (CAG) review during follow-up; (7) patients with CCTA findings suspicious for ISR who did not undergo confirmatory CAG during follow-up; and (8) patients with definite coronary lesion progression during follow-up who declined the recommended repeat revascularization procedure. The specific flow is shown in Figure 1.

Data Collection and Definitions

Patients' baseline examination data were collected from the hospital medical record information system. Patients were admitted to the hospital and fasting blood was collected for fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TG, high-sensitivity C-reactive protein (hs-CRP), and plasma creatinine (PCr).

The diagnosis of CCS was based on the guidelines.[4] Body mass index (BMI) = weight (kg)/height^2 (m^2). Diabetes mellitus is defined as a glycosylated hemoglobin ≥ 6.5%, FBG ≥ 7.0 mmol/L, or using hypoglycemic medications.[16] Hypertension was defined as a blood pressure ≥ 140/90 mmHg on multiple measurements.[17] Dyslipidemia was diagnosed as LDL-C ≥ 3.4 mmol/L, TG ≥ 1.7 mmol/L, and HDL-C < 1.0 mmol/L, or on lipid-lowering therapy.[18] Estimated glomerular filtration rate (eGFR) is based on the formula: $186 \times (PCr)^{-1.154} \times age^{-0.203} \times 0.742$ (if female) × 1.233 (if Chinese).[19]

Exposures

The exposure factor for study participants was the type of intervention treatment they received. GDMT was defined as

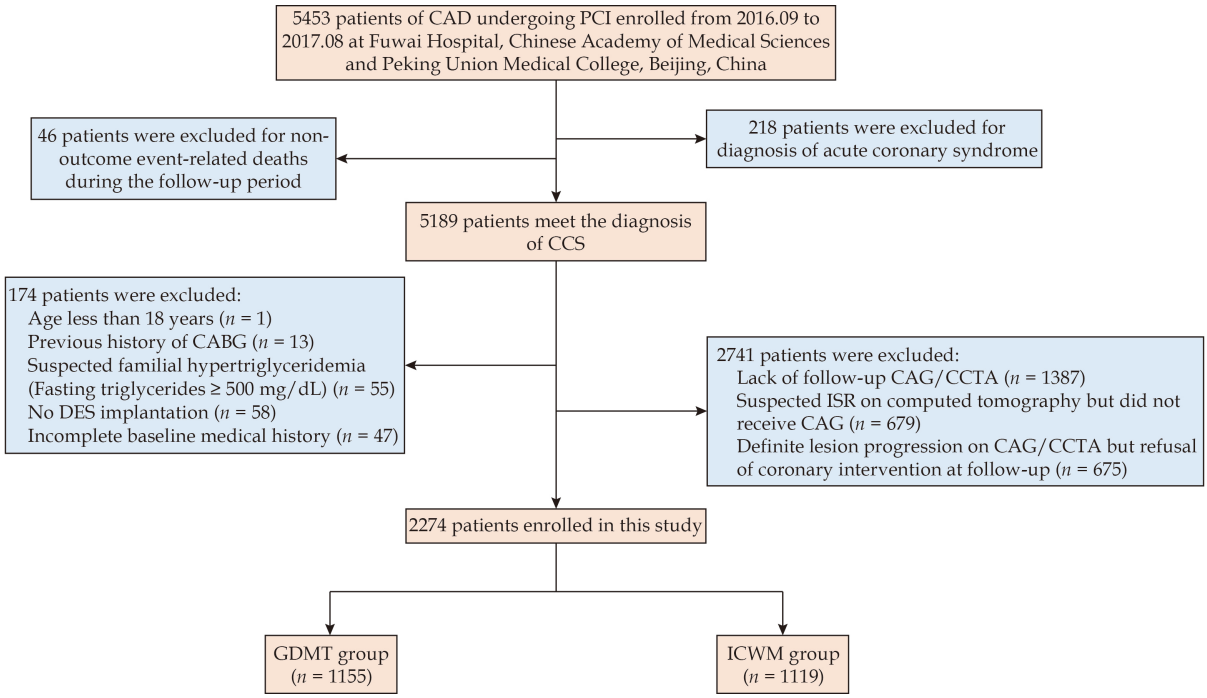

Figure 1 Flow chart for participant selection of this study. CAD: coronary artery disease; CAG: coronary angiography; CCS: chronic coronary syndrome; CCTA: coronary computed tomography angiography; DES: drug-eluting stent; GDMT: guideline-directed medical treatment; ICWM: integrative Chinese and Western medicine; ISR: in-stent restenosis; PCI: percutaneous coronary intervention.

receiving medication recommended by the guideline "2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes",[3] and receiving only western medications. ICWM is defined as adjunctive therapy with CHM to conventional western medications, with cumulative CHM treatment duration exceeding 6 months per year. CHM includes decoctions and Chinese patent medicines (supplemental material, Table 1S). Decoctions are typically composed of various herbs, such as Trichosanthes kirilowii Maxim (Gualou), Allium chinense (Xiebai), Panax notoginseng (Sanqi), and Angelica sinensis (Danggui), etc. The CHM intervention in this study was based on the "Guidelines for diagnosis and treatment of coronary heart disease and angina before and after intervention".[20] Common syndromes treated included qi deficiency, blood stasis, and phlegm accumulation, among others (supplemental material, Table 2S). The specific herbal formula and dosage for each patient were determined by experienced clinical TCM physicians based on individualized treatment principles. The decision on whether CHM prescriptions contributed to the improvement of CCS was evaluated by specialized TCM practitioners. Chinese patent medicines are pre-packaged CHM formulations approved for marketing by China Food and Drug Administration. According to follow-up records, the Chinese patent medicines used by patients in this study cohort included Tongxinluo Capsules, Qishen Capsules, Shexiang Baoxin Pills, and Compound Danshen Dripping Pills. The dosages of these Chinese patent medicines followed the recommended guidelines provided in the product instructions. Patients who met the CHM exposure criteria were selected into the ICWM group, and those who received only western medicines were entered into the GDMT group.

Endpoints and Follow-up

The primary endpoint was the composite of repeat revascularization and ISR, prespecified to reflect lesion-related residual risk after PCI in patients with CCS. Repeat revascularization and ISR were also analyzed separately as secondary endpoints. Follow-up occurred at 6, 12, 18, 24, 36, 48, and 60 months after hospital discharge, as well as in October 2022 (time window ± 14 days), through outpatient visits or telephone interviews. To assess the robustness of the main findings, a sensitivity analysis was performed using conventional major adverse cardiovascular events (MACE), defined as a composite of all-cause death, non-fatal MI, and stroke, based on the 23.98-month follow-up data from the original cohort (supplemental material, Tables 3S & 4S and Figure 1S). This sensitivity analysis was designed as a relatively independent robus-

tness check using a conventional hard-endpoint framework.

Repeat revascularization was defined as any objectively performed revascularization procedure during follow-up, including bare-metal stent implantation, DES implantation, plain balloon angioplasty, drug-coated balloon angioplasty, and coronary artery bypass grafting. Decisions regarding repeat revascularization were made jointly by cardiologists and patients. To avoid bias, patients who underwent staged PCI during the index admission were excluded. ISR was defined as the presence of ≥ 50% diameter stenosis within 5 mm of the in-stent segment or stent edge. Given the high specificity of CCTA, patients without ISR suggested by CCTA were included, whereas patients with CCTA findings suspicious for ISR were required to undergo confirmatory CAG for endpoint adjudication. Accordingly, cases without confirmatory CAG were not counted as ISR events, and patients with definite coronary lesion progression who did not ultimately undergo repeat revascularization were not counted as repeat revascularization events. After successful DES implantation, all patients underwent CAG or CCTA review at Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, and the results were interpreted by both cardiologists and imaging physicians.

Statistical Analysis

For normally distributed continuous variables, mean ± SD was used, otherwise medians (interquartile range) was used. The independent Student's *t*-test or the Kruskal-Wallis test was used for comparison between groups. For categorical variables, counts (percentages) were used. The Pearson's chi-squared test was used for comparisons between groups.

Time-to-event outcomes were compared between groups using the log-rank test and are presented with Kaplan-Meier curves. Multivariable Cox regression models were used to analyze the hazard ratio (HR) with 95% CI of associations between exposure factors and endpoint events. The multivariable models were constructed as follows: Model 1 was unadjusted, while Model 2 adjusted for age, sex, BMI, cigarette smoking, eGFR, and hs-CRP. Based on Model 2, Model 3 further adjusted for LDL-C, TG, FBG, prior PCI, presence of peripheral arterial disease, target lesion ≥ 20 mm, and number of stents. These additional covariates were selected based on clinical relevance, baseline imbalance, and previous literature, and were intended to account for residual cardiovascular risk related to lipid metabolism, glucose metabolism, systemic atherosclerotic burden, and lesion-/stent-related procedural complexity. Variance inflation factors for all covariates included in the multivariable models were < 3, indicating no significant multicollinearity.[21] Subgroup analyses were performed based on Model 3. Statistical analyses and figure plotting were conducted using SPSS 25.0 (SPSS Inc., IBM, Armonk, NY, USA) and R statistical software 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

From September 2016 to August 2017, a total of 5453 patients with CAD underwent PCI, of which 2274 patients fulfilled the diagnosis of CCS and were included in the final statistical analysis. There were 1155 patients in the GDMT group with a median age of 58.00 (52.00–64.00) years and 904 patients (78.3%) were males, 1119 patients in the ICWM group with a median age of 59.00 (52.00–66.00) years and 863 patients (77.10%) were males. Table 1 shows the baseline characteristics of the total study population grouped according to treatment strategies. There were no significant differences between the two groups in terms of gender, smoking history, medical history (including hypertension, previous MI, previous stroke, previous PCI, family history of CAD, multivessel CAD), laboratory findings (including HDL-C and TG), or angiographic results (including left main lesions, right coronary artery lesions, left anterior descending lesions, calcification of target lesions, chronic total occlusions, lesions > 20 mm long), as well as medication use (including dual antiplatelet therapy, statins, beta-blockers, insulin, and oral hypoglycemic drugs). However, statistically significant differences were observed between the two groups in the prevalence of diabetes mellitus, hyperlipidemia, peripheral arterial disease, as well as in BMI, TC, LDL-C, TC/HDL-C ratio, FBG, hs-CRP levels, left circumflex lesions, trifurcation/bifurcation lesions, restenotic lesions, and the use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker medications. Since the left ventricular ejection fraction, PCr and eGFR of both groups were in the normal range, the significant differences between the two groups could be considered not clinically significant ($P < 0.05$). In terms of the average number of stents implanted per case, although there was a statistical difference between the two groups ($P < 0.001$), the medians of the two groups were equal, and only the interquartile range had a distributional difference, suggesting that the difference was caused by the extreme values in the GDMT group, which did not reflect the actual situation in the two groups.

Table 1 Baseline characteristics of patients grouped according to treatment strategies.

Variable	GDMT group (*n* = 1155)	ICWM group (*n* = 1119)	*P*-value
Demographics			
Age, yrs	58.00 (52.00–64.00)	59.00 (52.00–66.00)	0.012
Male	904 (78.30%)	863 (77.10%)	0.512
Body mass index, kg/m^2	25.71 (23.89–27.78)	25.97 (24.07–28.08)	0.048
Risk factors			
Cigarette smoking	711 (61.60%)	657 (58.70%)	0.166
Diabetes mellitus	481 (41.60%)	390 (34.90%)	0.001
Hypertension	741 (64.20%)	742 (66.30%)	0.281
Dyslipidemia	1140 (98.70%)	882 (78.80%)	< 0.001
Previous MI	185 (16.00%)	200 (17.90%)	0.238
Previous stroke	133 (11.50%)	121 (10.80%)	0.595
Previous PCI	356 (30.80%)	315 (28.20%)	0.162
Peripheral arterial disease	161 (13.90%)	124 (11.10%)	0.040
Family history of CAD	203 (17.60%)	223 (19.90%)	0.151
Clinical presentations			
Multi-vessel CAD	937 (81.10%)	894 (79.90%)	0.458
Left ventricular ejection fraction, %	64.00 (60.00–66.00)	63.00 (60.00–65.00)	< 0.001
Laboratory measurements			
TC, mmol/L	3.81 (3.27–4.43)	3.96 (3.34–4.73)	< 0.001
LDL-C, mmol/L	2.19 (1.77–2.73)	2.33 (1.83–2.99)	< 0.001
HDL-C, mmol/L	1.04 (0.90–1.25)	1.06 (0.89–1.25)	0.999
TG, mmol/L	1.42 (1.08–1.95)	1.47 (1.09–2.02)	0.253
TG/HDL-C	1.35 (0.95–2.03)	1.41 (0.98–2.06)	0.223
TC/HDL-C	3.54 (3.01–4.25)	3.74 (3.07–4.56)	< 0.001
FBG, mmol/L	5.59 (5.00–6.80)	5.74 (5.10–7.01)	0.009
PCr, μmol/L	79.65 (70.37–89.44)	78.08 (68.48–89.35)	0.024
eGFR, mL/min per 1.73 m^2	107.67 (95.05–121.83)	110.87 (94.95–125.47)	0.022
hs-CRP, mg/L	2.28 (1.62–3.73)	1.75 (0.95–3.63)	< 0.001
Angiographic findings			
Left main lesions	55 (4.76%)	59 (5.27%)	0.577
Left anterior descending lesions	644 (55.76%)	586 (52.37%)	0.105
Left circumflex lesions	319 (27.62%)	260 (23.24%)	0.016
Right coronary artery lesions	519 (44.94%)	490 (43.79%)	0.582
Trifurcation/Bifurcation lesions	684 (59.22%)	613 (54.78%)	0.033
Restenotic lesions	25 (2.20%)	67 (6.00%)	< 0.001
Calcification of target lesions	587 (50.80%)	568 (50.80%)	0.976
Chronic total occlusions	187 (16.20%)	180 (16.10%)	0.946
Lesions > 20 mm	911 (78.90%)	855 (76.40%)	0.158
Length of stent, mm	36.00 (21.00–59.00)	32.00 (20.00–52.00)	< 0.001
Number of stents	2.00 (1.00–3.00)	2.00 (1.00–2.00)	< 0.001
Medications at discharge			
Dual antiplatelet therapy	1153 (99.80%)	1115 (99.60%)	0.445
Statins	1143 (99.00%)	1098 (98.10%)	0.095

Continued

Variable	GDMT group (n = 1155)	ICWM group (n = 1119)	P-value
Angiotensin-converting enzyme inhibitor/Angiotensin II receptor blocker	572 (49.50%)	644 (57.60%)	< 0.001
Beta-blockers	968 (83.80%)	965 (86.20%)	0.105
Insulin	129 (11.20%)	128 (11.40%)	0.839
Oral hypoglycemic drugs	299 (25.90%)	298 (26.60%)	0.687
Endpoint events			
The primary endpoint	575 (49.80%)	479 (42.80%)	0.001
Repeat revascularization	529 (45.80%)	455 (40.70%)	0.013
ISR	258 (22.30%)	225 (20.10%)	0.194

Data are presented as median (interquartile range) or n (%). CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; GDMT: guideline-directed medical treatment; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; ICWM: integrative Chinese and Western medicine; ISR: in-stent restenosis; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; PCI: percutaneous coronary intervention; PCr: plasma creatinine; TC: total cholesterol; TG: triglycerides.

Outcomes

Association between treatment strategies and the primary endpoint

For the primary endpoint, the median duration of follow-up in the study population was 60.45 (16.47–68.00) months. During follow-up, 1054 patients (46.40%) experienced the primary endpoint, including 479 patients (42.80%) in the ICWM group and 575 patients (49.80%) in the GDMT group. Kaplan-Meier survival analysis showed that the cumulative incidence of the primary endpoint was significantly lower in the ICWM group than in the GDMT group (Figure 2A, log-rank P < 0.001).

The results of the multivariable Cox regression analysis are shown in Table 2. Compared with the GDMT group, the ICWM group was associated with a 22.20% lower risk of the pr-

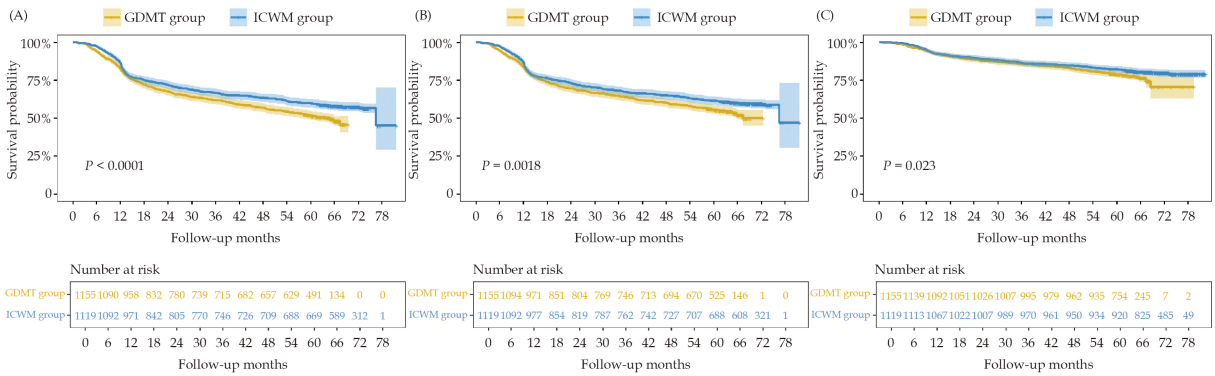

Figure 2 Kaplan-Meier survival analysis for the association of treatment strategies with post-PCI adverse cardiovascular events. (A) The primary endpoint; (B) repeat revascularization; and (C) in-stent restenosis. GDMT: guideline-directed medical treatment; ICWM: integrative Chinese and Western medicine; PCI: percutaneous coronary intervention.

Table 2 The association between treatment strategies and the primary endpoint.

	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
GDMT	Reference		Reference		Reference	
ICWM	0.778 (0.689–0.879)	< 0.001	0.781 (0.691–0.884)	< 0.001	0.741 (0.654–0.841)	< 0.001

Model 1: unadjusted any variables. Model 2: adjusted for age, sex, BMI, cigarette smoking, eGFR, and hs-CRP. Model 3: adjusted for variables in Model 2 plus the LDL-C, TG, FBG, prior PCI, presence of peripheral arterial disease, target lesion ≥ 20 mm, and number of stents. BMI: body mass index; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; GDMT: guideline-directed medical treatment; hs-CRP: high-sensitivity C-reactive protein; ICWM: integrative Chinese and Western medicine; LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention; TG: triglycerides.

imary endpoint in Model 1 (HR = 0.778, 95% CI: 0.689–0.879, P < 0.001). The association remained significant in Model 2 (adjusted HR = 0.781, 95% CI: 0.691–0.884, P < 0.001) and after full adjustment in Model 3 (adjusted HR = 0.741, 95% CI: 0.654–0.841, P < 0.001).

Association between treatment strategies and secondary outcomes

For repeat revascularization, the median follow-up duration was 61.23 (17.97–68.71) months. During the follow-up, 984 patients (43.30%) experienced repeat revascularization, including 529 patients (45.80%) in the GDMT group and 455 patients (40.70%) in the ICWM group. Kaplan-Meier survival analysis showed that the cumulative incidence of repeat revascularization was significantly lower in the ICWM group than in the GDMT group (Figure 2B, log-rank P = 0.0018).

As shown in Table 3, compared with the GDMT group, the ICWM group was associated with an 18.2% lower risk of repeat revascularization in Model 1 (HR = 0.818, 95% CI: 0.721–0.928, P = 0.002). The association remained significant in Model 2 (adjusted HR = 0.824, 95% CI: 0.726–0.936, P = 0.003) and after full adjustment in Model 3 (adjusted HR = 0.781, 95% CI: 0.686–0.889, P < 0.001).

For ISR, the median follow-up duration was 65.53 (59.40–71.57) months. A total of 483 patients (21.20%) experienced ISR during the follow-up period, of which 258 patients (22.30%) were in the GDMT group and 225 patients (20.10%) were in the ICWM group. Kaplan-Meier survival analysis showed that the cumulative incidence of ISR was significantly lower in the ICWM group than in the GDMT group (Figure 2C, log-rank P = 0.023).

The results of the multivariable Cox regression analysis for ISR are shown in Table 4. In Model 1 and Model 2, ICWM was associated with 19.0% (HR = 0.810, 95% CI: 0.675–0.971, P = 0.023) and 19.5% (adjusted HR = 0.805, 95% CI: 0.671–0.966, P = 0.020) lower risks of ISR than GDMT, respectively. The association remained significant after full adjustment in Model 3, with ICWM associated with a 17.5% lower risk of ISR (adjusted HR = 0.825, 95% CI: 0.686–0.993, P = 0.042).

Subgroup analysis of treatment strategies and primary endpoint

Subgroup analyses showed significant interactions between treatment strategy and prior PCI ($P_{interaction}$ = 0.006) as well as multivessel CAD ($P_{interaction}$ = 0.003) with respect to the primary endpoint. In patients with prior PCI, ICWM was associated with a 41% lower risk of the primary endpoint than GDMT (adjusted HR = 0.59, 95% CI: 0.48–0.73, P < 0.001), whereas in those without prior PCI, the association was weaker (adjusted HR = 0.84, 95% CI: 0.71–0.98, P = 0.03). Similarly, ICWM was associated with a lower risk of the primary endpoint in both patients with and without multivessel CAD, with a more pronounced association observed in those without multivessel disease (adjusted HR = 0.46, 95% CI: 0.32–0.68, P < 0.001) than in those with multivessel CAD (adjusted HR = 0.81, 95% CI: 0.71–0.93, P = 0.002). No significant in-

Table 3 The association between treatment strategies and the repeat revascularization.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
GDMT	Reference		Reference		Reference	
ICWM	0.818 (0.721–0.928)	0.002	0.824 (0.726–0.936)	0.003	0.781 (0.686–0.889)	< 0.001

Model 1: unadjusted any variables. Model 2: adjusted for age, sex, BMI, cigarette smoking, eGFR, and hs-CRP. Model 3: adjusted for variables in Model 2 plus the LDL-C, TG, FBG, prior PCI, presence of peripheral arterial disease, target lesion ≥ 20 mm, and number of stents. BMI: body mass index; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; GDMT: guideline-directed medical treatment; hs-CRP: high-sensitivity C-reactive protein; ICWM: integrative Chinese and Western medicine; LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention; TG: triglycerides.

Table 4 The association between treatment strategies and the in-stent restenosis.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
GDMT	Reference		Reference		Reference	
ICWM	0.810 (0.675–0.971)	0.023	0.805 (0.671–0.966)	0.020	0.825 (0.686–0.993)	0.042

Model 1: unadjusted any variables. Model 2: adjusted for age, sex, BMI, cigarette smoking, eGFR, and hs-CRP. Model 3: adjusted for variables in Model 2 plus the LDL-C, TG, FBG, prior PCI, presence of peripheral arterial disease, target lesion ≥ 20 mm, and number of stents. BMI: body mass index; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; GDMT: guideline-directed medical treatment; hs-CRP: high-sensitivity C-reactive protein; ICWM: integrative Chinese and Western medicine; LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention; TG: triglycerides.

teractions were observed in the other prespecified subgroups (Figure 3).

DISCUSSION

This prospective cohort study evaluated the association between adjunctive CHM and post-PCI adverse cardiovascular outcomes in patients with CCS. The main findings were as follows. Firstly, compared with GDMT alone, ICWM was associated with a significantly lower risk of the primary composite endpoint of repeat revascularization and ISR. Secondly, this association remained consistent when the individual components of the composite endpoint were analyzed separately, with lower risks observed for both repeat revascularization and ISR. Thirdly, the sensitivity analysis using conventional MACE showed a directionally consistent benefit, suppo-

Variable	Count	Percent	HR (95% CI)	*P*-value	$P_{interaction}$-value
Age, yrs					0.255
< 65	1673	73.57%	0.77 (0.66–0.89)	0.001	
≥ 65	601	26.43%	0.66 (0.52–0.84)	0.001	
Gender					0.970
Female	507	22.30%	0.78 (0.59–1.03)	0.082	
Male	1767	77.70%	0.74 (0.64–0.85)	< 0.001	
BMI, kg/m^2					0.848
≤ 24	572	25.15%	0.74 (0.56–0.97)	0.031	
> 24	1702	74.85%	0.75 (0.65–0.86)	< 0.001	
Smoke					0.566
No	906	39.84%	0.77 (0.63–0.94)	0.010	
Yes	1368	60.16%	0.73 (0.62–0.86)	< 0.001	
Family history of CAD					0.241
No	1848	81.27%	0.71 (0.62–0.82)	< 0.001	
Yes	426	18.73%	0.88 (0.65–1.19)	0.401	
Dyslipidemia					0.851
No	252	11.08%	0.65 (0.30–1.40)	0.269	
Yes	2022	88.92%	0.72 (0.62–0.82)	< 0.001	
Hypertension					0.325
No	791	34.78%	0.69 (0.54–0.87)	0.002	
Yes	1483	65.22%	0.76 (0.66–0.89)	< 0.001	
Previous MI					0.469
No	1889	83.07%	0.75 (0.65–0.87)	< 0.001	
Yes	385	16.93%	0.66 (0.50–0.87)	0.003	
Previous stroke					0.762
No	2020	88.83%	0.73 (0.64–0.84)	< 0.001	
Yes	254	11.17%	0.87 (0.60–1.27)	0.476	
Previous PCI					0.006
No	1603	70.49%	0.84 (0.71–0.98)	0.030	
Yes	671	29.51%	0.59 (0.48–0.73)	< 0.001	
Multi-vessel CAD					0.003
No	443	19.48%	0.46 (0.32–0.68)	< 0.001	
Yes	1831	80.52%	0.81 (0.71–0.93)	0.002	
Left ventricular ejection fraction, %					0.110
< 50	112	4.93%	0.43 (0.24–0.78)	0.006	
≥ 50	2162	95.07%	0.75 (0.66–0.86)	< 0.001	

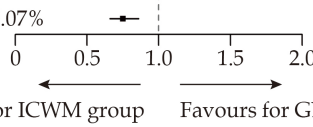

Figure 3 Subgroup analysis of the association between treatment strategies and the risk of post-PCI adverse cardiovascular events. Adjustments were made for age, sex, BMI, cigarette smoking, eGFR, hs-CRP, LDL-C, TG, FBG, prior PCI, presence of peripheral arterial disease, target lesion ≥ 20 mm, and number of stents in the multivariable model. BMI: body mass index; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; GDMT: guideline-directed medical treatment; hs-CRP: high-sensitivity C-reactive protein; ICWM: integrative Chinese and Western medicine; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; PCI: percutaneous coronary intervention; TG: triglycerides.

rting the robustness of the main findings. Last but not least, subgroup analyses suggested that patients with prior PCI and those without multivessel CAD may derive greater benefit from ICWM.

The rationale for selecting the primary endpoint should be understood in the context of the specific clinical question addressed in this study. In CCS patients after PCI, repeat revascularization and ISR are more directly related to lesion progression and residual post-PCI risk than traditional hard endpoints. In clinically stable CCS, death and MI occur relatively less frequently during follow-up and are influenced by multiple systemic factors, whereas repeat revascularization and ISR more sensitively reflect the long-term need for further coronary intervention after the index PCI. This also helps explain the relatively high event rate observed in our cohort. The study population had substantial angiographic complexity, including high proportions of multivessel disease (81.1%), bifurcation/trifurcation lesions (59.22%), and long lesions (78.9%), all of which are associated with elevated risks of restenosis and repeat intervention. In addition, unlike conventional MACE definitions, our primary endpoint was intentionally designed to capture lesion-related events that are expected to occur more frequently during long-term follow-up. Importantly, even against this high-risk angiographic background, adjunctive CHM remained associated with a significantly lower risk of the primary endpoint after full adjustment, underscoring the potential clinical relevance of ICWM in the long-term management of selected CCS patients after PCI.

To further test the robustness of the findings beyond these post-PCI adverse cardiovascular events, we additionally performed a sensitivity analysis using conventional MACE, defined in this study as a composite of all-cause death, non-fatal MI, and stroke. The sensitivity analysis served a different purpose from the primary endpoint analysis, as it was intended to provide a relatively independent robustness check using a more conventional hard-endpoint framework. For this reason, repeat or unplanned revascularization was not included in the MACE definition to avoid substantial conceptual overlap with the primary endpoint, whereas stroke was retained as a systemic atherosclerotic event. Notably, the association between ICWM and a lower risk of MACE remained significant after full adjustment, suggesting that the observed benefit was not confined to post-PCI lesion-related events alone.

The present findings are broadly consistent with previous studies suggesting that CHM may be of value as an adjunct therapy after PCI, with lower risks of MACE reported in patients receiving integrative therapy.[22-25] This study extends the evidence by focusing specifically on CCS rather than a broader CAD spectrum, by evaluating post-PCI adverse cardiovascular events that directly reflect lesion-related progression, and by providing relatively long-term follow-up. Importantly, in this CCS cohort, ICWM was associated not only with a lower risk of the primary composite endpoint (adjusted HR = 0.741, 95% CI: 0.654–0.841), but also with a lower risk of conventional MACE in the sensitivity analysis (adjusted HR = 0.561, 95% CI: 0.356–0.885). Taken together, these findings suggest that adjunctive CHM may contribute not only to symptom control, but also to long-term secondary prevention after PCI in selected CCS patients.

When interpreting these favorable outcomes, a key methodological issue is the inherent heterogeneity of CHM interventions in real-world TCM practice. To address this issue while maintaining clinical relevance, we adopted a standardized yet individualized treatment strategy, allowing syndrome differentiation at the patient level within a prespecified, guideline-informed therapeutic framework. All prescriptions were based on the "Guidelines for diagnosis and treatment of coronary heart disease and angina before and after intervention" and the "Expert consensus on integrated Chinese and Western medicine rehabilitation treatment for stable coronary heart disease".[20,26] As shown in supplemental material, Table 1S, 63.63% of patients received individualized decoctions, whereas the remainder were treated with standardized Chinese patent medicines. Thus, although the specific formulations varied across patients, the overall treatment strategy remained clinically coherent and reflective of real-world TCM practice.

Regarding the individual components of the primary endpoint, ICWM was associated with lower risks of both repeat revascularization and ISR after multivariable adjustment, with a more robust association observed for repeat revascularization. The association with ISR remained significant across models but showed a relatively modest effect size in the fully adjusted analysis. Clinically, these findings suggest that the potential benefit of CHM may not be confined to a single pathway such as local neointimal suppression, but may instead reflect a broader influence on the post-PCI disease milieu, including inflammation, endothelial dysfunction, microcirculatory impairment, and progression of residual atherosclerotic risk.[27-31] Such an interpretation is biologically plausible and consistent with the multi-component, multi-target characteristics of CHM, although the underlying mechanisms still require further investigation.[32]

Furthermore, subgroup analysis suggested that patients

with prior PCI and those without multivessel disease might derive greater benefit from ICWM. The more pronounced association observed in patients with prior PCI may indicate that adjunctive CHM is particularly relevant in individuals with a higher cumulative burden of vascular injury, repeated intervention, and persistent residual risk. Likewise, the greater apparent benefit in patients without multivessel disease may suggest that CHM is more effective when introduced at a relatively earlier stage of anatomical disease complexity, before the disease burden becomes more extensive. Although these subgroup findings should be interpreted cautiously, they may help generate hypotheses for more individualized integrative treatment strategies in future studies.

LIMITATIONS

Several limitations should be acknowledged. Firstly, this was a single-center observational study, and causal inference cannot be established despite prospective follow-up and multivariable adjustment. Although the fully adjusted model incorporated relevant covariates, residual confounding from unmeasured factors cannot be fully excluded; in particular, lipoprotein(a), an important residual cardiovascular risk marker, was not routinely collected in the parent cohort established in 2016–2017 and therefore could not be included in the present analysis. Secondly, because patients with severe hypertriglyceridemia were excluded according to the predefined parent-cohort criteria, the generalizability of the findings to this subgroup may be limited. Thirdly, patients with suspected ISR without confirmatory CAG and those with definite lesion progression who declined repeat revascularization were excluded to ensure strict endpoint adjudication; although this approach reduced endpoint misclassification, it may also have introduced selection bias. Fourthly, exposure to CHM was defined as a long-term treatment strategy, but more granular information on the dosage of individualized decoctions, daily adherence, and differences among specific CHM formulations was not available. Last but not least, future multicenter studies, ideally with more detailed exposure assessment and randomized designs, are warranted to validate and extend these findings.

CONCLUSIONS

In this prospective cohort study, adjunctive CHM was associated with lower risks of the composite endpoint of repeat revascularization and ISR, as well as its individual components, in patients with CCS after PCI. This association remained directionally consistent in the sensitivity analysis using conventional MACE. The observed benefit appeared to be more pronounced in patients with prior PCI and those without multivessel CAD. Taken together, these findings suggest that CHM may be a useful adjunctive strategy for long-term management after PCI in selected CCS patients.

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