

Effects of adjuvant Chinese patent medicine therapy on major adverse cardiovascular events in patients with coronary heart disease angina pectoris: a population-based retrospective cohort study

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Abstract

Objective: This study aimed to explore the effects of Chinese patent medicine (CPM) in reducing the incidence of major adverse cardiovascular events (MACE) in patients with coronary heart disease (CHD) angina pectoris and improving clinical effectiveness and provide evidence for its use as clinical adjuvant therapy.

Methods: Twenty-eight thousand five hundred and seventeen patients hospitalized with CHD angina pectoris from 6 hospitals were divided into CPM group ($n=11,374$) and non-CPM group ($n=17,143$) to evaluate the incidence of MACE, including myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting.

Results: The incidence of MACE in the CPM group was lower than that in the non-CPM group. CPM therapy was an independent protective factor that reduced the overall risk of MACE [adjusted hazard ratio = 0.40, 95% confidence interval (0.33; 0.49)]. Patients in the CPM group who received one, two, or three types of CPM could benefit from adjuvant treatment with CPM, and taking more types of CPM was associated with a lower risk of MACE. In addition, the male population was better than the female population at taking CPM, and middle-aged people aged 55 to 64 were more suited to take CPM based on Western medicine.

Conclusions: The use of CPM as adjuvant therapy can decrease the occurrence of MACE in patients with CHD angina pectoris, especially in men and middle-aged people, and the drug treatment plan should be optimized accordingly. However, this conclusion needs further verification by prospective cohort studies in the future.

Keywords: Chinese patent medicine, Coronary heart disease angina pectoris, Major adverse cardiovascular events, Retrospective cohort study

Introduction

Atherosclerotic cardiovascular disease remains the leading cause of mortality globally, accounting for approximately 30% of all deaths^[1]. Coronary heart disease (CHD), a cardiovascular disease caused by atherosclerosis^[2], leads to more than 8.9 million deaths in 2017^[3] that represents a globally increasing public health burden^[4]. Angina pectoris is a symptom of CHD, usually defined as pain or discomfort in (or adjacent to) the chest, which is typically provoked by exertion or anxiety. The American College of Cardiology and the American Heart Association guidelines primarily

recommend antiplatelet therapy, anticoagulant therapy, and anti-ischemic therapy^[5–6]. They have certain clinical effects, but there is an unmet need for controlling the progression of angina, and most patients will suffer from myocardial infarction or undergo revascularization^[7–8]. To improve the quality of life, increase the survival rate, and prolong the survival period, some patients will adopt complementary and alternative therapies^[9].

Traditional Chinese medicine (TCM) has a long history of CHD prevention and treatment with recorded effects^[10]. With the development of modern drug preparation technologies, more Chinese patent medicines (CPMs) have been developed to meet the needs of TCM syndrome differentiation and facilitate personal use. *The Chinese National Essential Drug*^[11], *the Pharmacopeia of the People's Republic of China*^[12], and the China Food and Drug Administration maintain lists of various TCM preparations (mixtures of multi-herbs) subjected to relatively strict drug evaluation processes, which are widely used in current clinical practice^[6]. These TCM preparations are considered as CPMs. More recently, TCM has received attention because of its diverse components, its actions on multiple targets and pathways, and overall, the regulatory role^[13]. Clinical practitioners have reported a significant effect of CPM on patients with angina pectoris when CPM is combined with Western medicine^[14]. It could be an option to optimize strategies for the prevention and treatment of angina pectoris. However, the current domestic and foreign clinical studies on CPM are mostly based on randomized

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controlled trials (RCTs), and the large-scale clinical studies without human intervention in restoring the true characteristics of CPM are limited. Although RCTs are considered to be the gold standard for determining causation between an exposure and an outcome, patients are selected by inclusion and exclusion criteria, which are poorly represented, have certain biases, and have many reasons for infeasibility^[15–16]. Cohort studies are large sample size studies conducted in a real-world setting, and the data collected are complete and reliable. The morbidity or mortality of the exposed and non-exposed groups can be obtained directly through follow-up records of event cases, which has certain advantages because cases and non-cases are from the same population, minimizing selection bias^[16]. Therefore, this study aims to explore the effects of CPM in reducing the incidence of major adverse cardiovascular events (MACE) and improving clinical effectiveness in CHD angina pectoris patients and provide evidence for their usage as clinical adjuvant therapy.

Methods

Study population

One hundred seven thousand three hundred and one CHD patients diagnosed between January 1, 2014 and September 30, 2020 were included from six hospitals, including First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Second Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin Chest Hospital, Nankai Hospital: Tianjin Hospital of Integrated Traditional Chinese and Western Medicine, Tianjin Medical University General Hospital,

and Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital (Supplementary Table 1, <http://links.lww.com/AHM/A15>). Data collection was performed *via* the hospital information system (HIS). The inclusion criteria were as follows: (1) age within 35 to 75 years without sex restrictions; (2) patients with CHD angina pectoris diagnosed between September 1, 2014, and September 1, 2019, which met the diagnostic criteria of Western medicine (Supplemental digital content, <http://links.lww.com/AHM/A15>); and (3) patients who met the criteria for drug treatment. The exclusion criteria were as follows: (1) coexistence of other cardiac diseases, neurosis, climacteric syndrome, hyperthyroidism, cervical spondylosis of spinal cord or vertebral artery type, gastroesophageal reflux disease, and esophageal hiatus hernia that may cause chest pain; (2) patients suffering from major diseases such as heart failure, myocarditis, cardiomyopathy, severe heart valve diseases, liver failure or renal failure, malignant tumors, and severe metabolic diseases and those with severe symptoms and uncontrollable angina pectoris; (3) pregnant women, lactating women, or women of childbearing age with fertility requirements; (4) mental patients or cognitive dysfunction; and (5) other conditions that the researchers considered inappropriate for the trial. We performed 1:1.5 matching between the CPM group (ie, CPM combined with the convention treatment of CHD angina pectoris using Western medicine) and the non-CPM group based on sex and age. Finally, 28,517 CHD angina pectoris patients were enrolled Figure 1, and a database, *Retrospective Cohort Study on Adjuvant Treatment of Coronary Heart Disease Angina Pectoris with Chinese Patent Medicine*, was established.

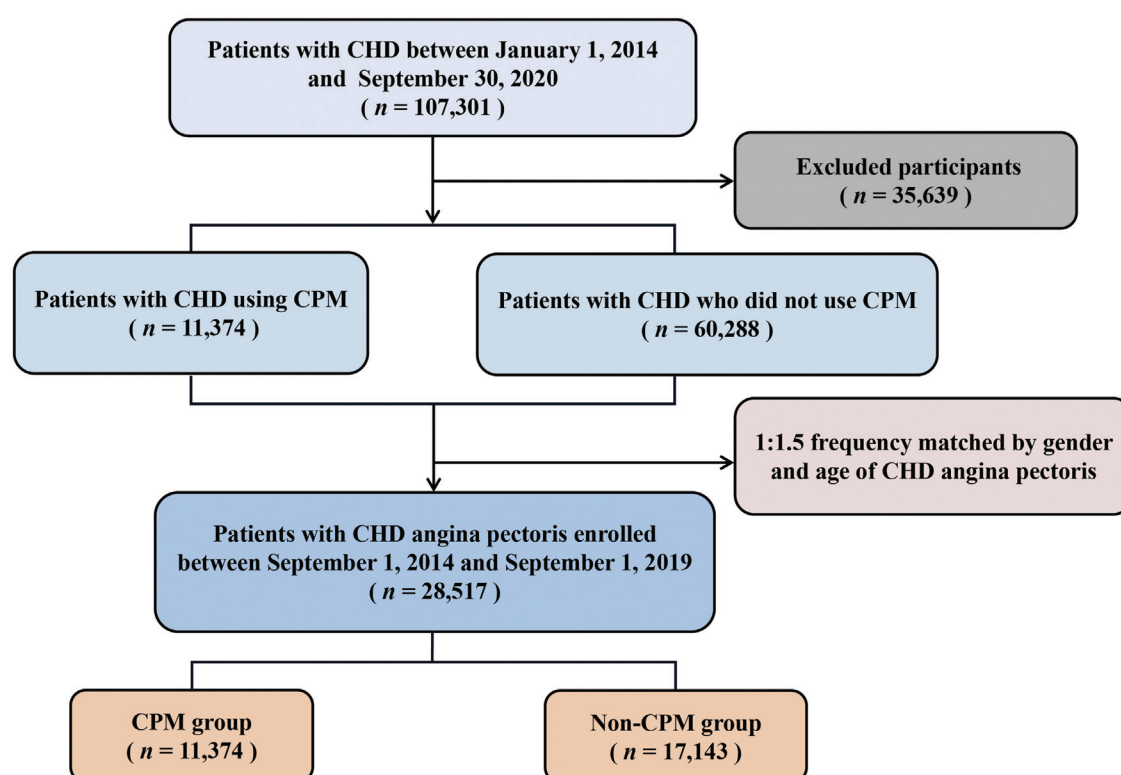


Figure 1. Outline of the identification and recruitment of the CHD angina pectoris study cohort in Tianjin six hospitals. CHD: coronary heart disease; CPM: Chinese patent medicine.

Ethics statement

This study was approved by the Ethics Committee of Tianjin University of Traditional Chinese Medicine (Lot Number: TJUTCM-EC20190008), and the requirement for informed consent was waived. This study was registered within the Clinical Trials.gov (registration number: NCT04026724) and the Chinese Clinical Trial Registry (registration number: ChiCTR1900024535).

Data collection

Data on sex, age, smoking history, alcoholic drinking history, family history of CHD, hypertension, hyperlipidemia, diabetes, current use of antianginal medication, anticoagulant medication, antihypertensive medication, antilipidemic medication, and antiarrhythmic medication were obtained from the HIS. The *International Classification of Diseases*, 10th revision (ICD-10) was utilized in the HIS since 1997. Smoking status was categorized as current versus former/never smoker, drinking was categorized as current versus former/never drinker, whereas family history of CHD was defined as the occurrence of CHD or myocardial infarction (MI) in at least one relative, or described as heart disease. Hypertension (ICD-10 codes I10-I15) was ascertained based on electronic medical record-reported history of hypertension or hypertension diagnosis, so were hyperlipidemia (ICD-10 code E78.501) and diabetes (ICD-10 codes E10-E14).

Assessment of CHD angina pectoris

Information on CHD diagnoses (ICD-10 codes I20, I24-I25, and I49-I50) was obtained from the HIS. Angina pectoris includes stable angina pectoris and unstable angina pectoris. According to the diagnostic criteria of CHD angina pectoris (Supplemental digital content, <http://links.lww.com/AHM/A15>), patients with angina pectoris cases were identified with at least one above-mentioned ICD code or more.

Definition of CPM group

CPM was used by the patients in addition to the conventional Western medicine administered during hospitalization (including at least 4–31 d of CPM administration during hospitalization). Under the guidance of the theory of TCM, the CPM was developed into a dosage form according to standards, using Chinese herbal medicine pieces that could be directly used to prevent and treat diseases as raw materials. Conventional Western medicines for CHD angina pectoris include antianginal medication, anticoagulant medication, antihypertensive medication, antilipidemic medication, and antiarrhythmic medication.

Study endpoint

The primary endpoint was the composite of MACE, including MI, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). The observation time lasted from patient enrollment to discharge or the end of this study.

Statistical analysis

The quantitative data was compared with a normal distribution (Kolmogorov-Smirnov method) and homo-

geneous variance (Levene method) using *t*-test, and expressed as mean±standard deviation (SD). Non-normally distributed quantitative data are expressed as medians with interquartile ranges. The qualitative data were compared using the chi-squared test or Fisher's exact test, and they are expressed as frequency (percentage). The survival curve of the patients was generated using the Kaplan-Meier method, and the incidences of MACE in the two groups were compared using the log-rank test. Cox proportional-hazards models were used to estimate the unadjusted and adjusted hazard ratios of CPM on the risk of MACE in patients with CHD angina pectoris.

Sex, age, smoking history, alcoholic drinking history, family history of CHD, hypertension, hyperlipidemia, and diabetes were considered as potential confounders in CHD angina pectoris. Missing values for smoking (*n*=10,840), drinking (*n*=11,018), family history of CHD (*n*=10,478), current antianginal medication (*n*=4,570), current anticoagulant medication (*n*=4,570), current antihypertensive medication (*n*=4,570), current antilipidemic medication (*n*=4,570), and current antiarrhythmic medication (*n*=4,570) were imputed by multiple imputation. IBM SPSS (version 24.0; IBM Corp, New York, NY, USA) was used as the statistical analysis tool.

Results

Characteristics of the study population

In total, 28,517 participants were enrolled during the study period; 11,374 (39.88%) received CPM therapy after the diagnosis of angina pectoris, and 17,143 (60.12%) did not receive CPM therapy. Compared with the non-CPM group, the CPM group had no statistical difference in sex, age, smoking, drinking, and current antihypertensive medication (Table 1).

Comparison of the incidence on the different types of MACE

Five subgroups were determined based on the types of MACE: composite MACE (*n*=480), MI (*n*=182), PCI (*n*=309), CABG (*n*=11), and revascularization (PCI or CABG, *n*=316). The incidences of MACE in these subgroups were 34.38%, 28.02%, 31.19%, 18.18%, and 37.66% in the CPM group and 65.63%, 71.98%, 61.81%, 81.82%, and 62.34% in the non-CPM group, respectively. The median follow-up time was 10 days. The Kaplan-Meier curve analysis showed that the incidence of MACE in the CPM group was lower than that in the non-CPM group (Figure 2).

The influence of CPM on the overall incidence of composite MACE

A multivariate Cox proportional-hazards model showed that adjuvant therapy with CPM was an independent protective factor for reducing the overall incidence of composite MACE in patients with angina pectoris [adjusted hazard ratio (HR)=0.40, 95% confidence interval (CI) (0.33; 0.49)] (Figure 3, Supplementary Table 2, <http://links.lww.com/AHM/A15>). Based on the type of CPM (Supplementary Tables 3–5, <http://links.lww.com/AHM/A15>), the CPM group was divided into three subgroups: the subgroups that used one type of CPM, two types of CPM, and three or more types of CPM. After adjusting the covariates, it was found that the

Table 1**Baseline characteristics of the study participants by CPM ($n=28,517$).**

Characteristics	CPM group $n=11,374$	Non-CPM group $n=17,143$	<i>P</i>
Male, n (%)	4,822 (42.39)	7,277 (42.45)	0.93
Age (mean $\pm$ SD, years)	63.03 $\pm$ 7.85	63.00 $\pm$ 7.83	0.76
Smoking history, n (%)	4,259 (37.45)	6,362 (37.11)	0.57
Alcohol drinking history, n (%)	2,941 (25.86)	4,300 (25.08)	0.14
Family history of CHD, n (%)	1,879 (16.52)	3,051 (17.80)	0.005
Hypertension, n (%)	7,605 (66.69)	7,686 (44.80)	<0.001
Hyperlipidemia, n (%)	4,944 (43.40)	4,038 (23.60)	<0.001
Diabetes, n (%)	4,941 (43.33)	4,277 (24.95)	<0.001
Current antianginal medication, n (%)	7,334 (64.48)	11,649 (67.95)	<0.001
Current anticoagulant medication, n (%)	9,367 (82.35)	14,434 (84.20)	<0.001
Current antihypertensive medication, n (%)	9,226 (81.11)	13,930 (81.26)	0.76
Current antilipidemic medication, n (%)	8,504 (74.77)	13,336 (77.79)	<0.001
Current antiarrhythmic medication, n (%)	510 (4.48)	1034 (6.03)	<0.001

CHD: coronary heart disease; CPM: Chinese patent medicine; SD: standard deviation.

use of more types of CPM was associated with a lower risk of MACE in patients with CHD angina pectoris.

Comparison of the overall risk of composite MACE in CHD angina pectoris patients with different sexes

According to sex, participants were divided into the male and female subgroups, and their overall risks of composite MACE were compared. The Kaplan-Meier curve analysis showed that the overall incidence of

composite MACE in both men and women in the CPM group was lower than that in the non-CPM group, and that in men was lower than that in women (Figure 4A and B). A multivariate Cox proportional-hazards model was used to analyze the effect of CPM adjuvant therapy on the overall incidence of composite MACE in patients with CHD angina pectoris of different sexes. The model showed that in men [adjusted HR=0.34, 95% CI (0.26; 0.44)] and women [adjusted HR=0.56, 95% CI (0.41; 0.78)] with CHD angina pectoris, adjuvant therapy with CPM was an independent protective factor for reducing

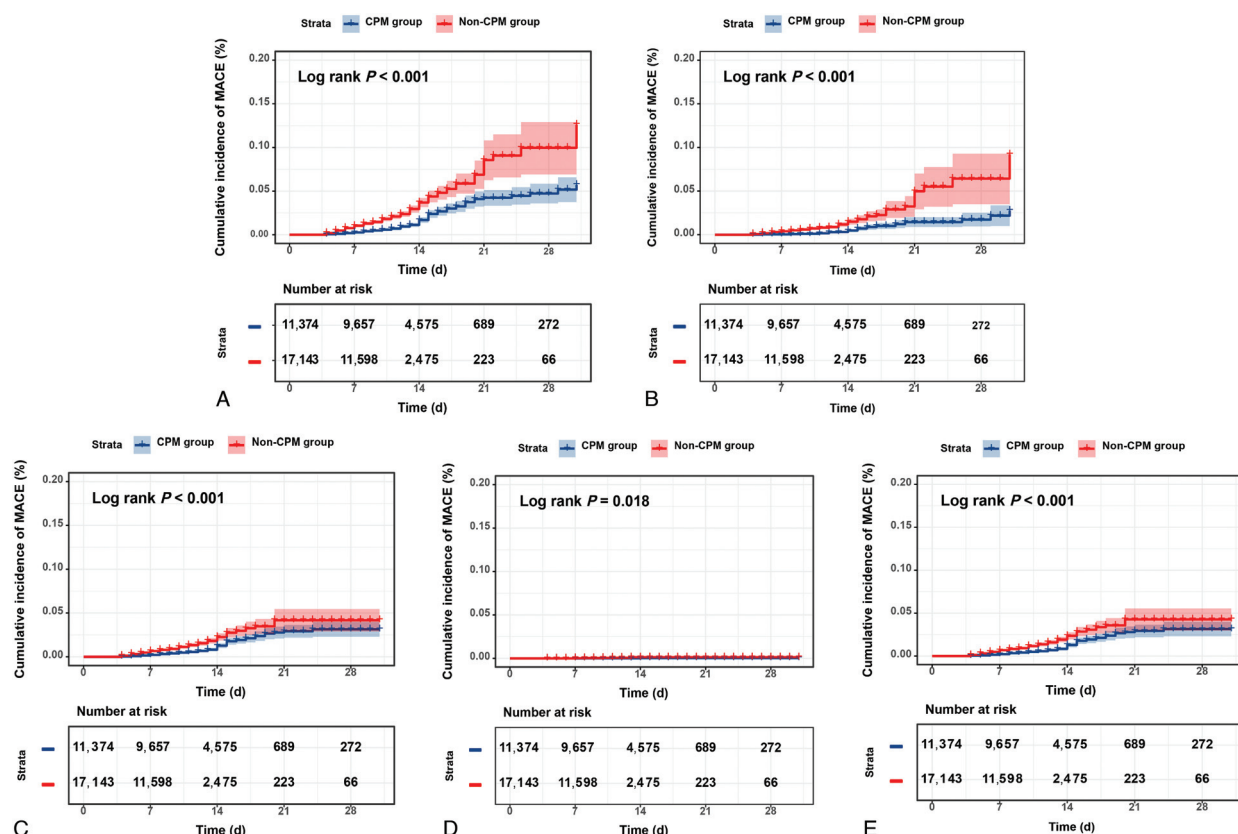


Figure 2. The incidence of MACE between CPM and non-CPM groups in patients with CHD angina pectoris. (A) Composite MACE. (B) MI. (C) PCI. (D) CABG. (E) Revascularization. CABG: coronary artery bypass grafting; CHD: coronary heart disease; CPM: Chinese patent medicine; MACE: major adverse cardiovascular events; MI: myocardial infarction; PCI: percutaneous coronary intervention.

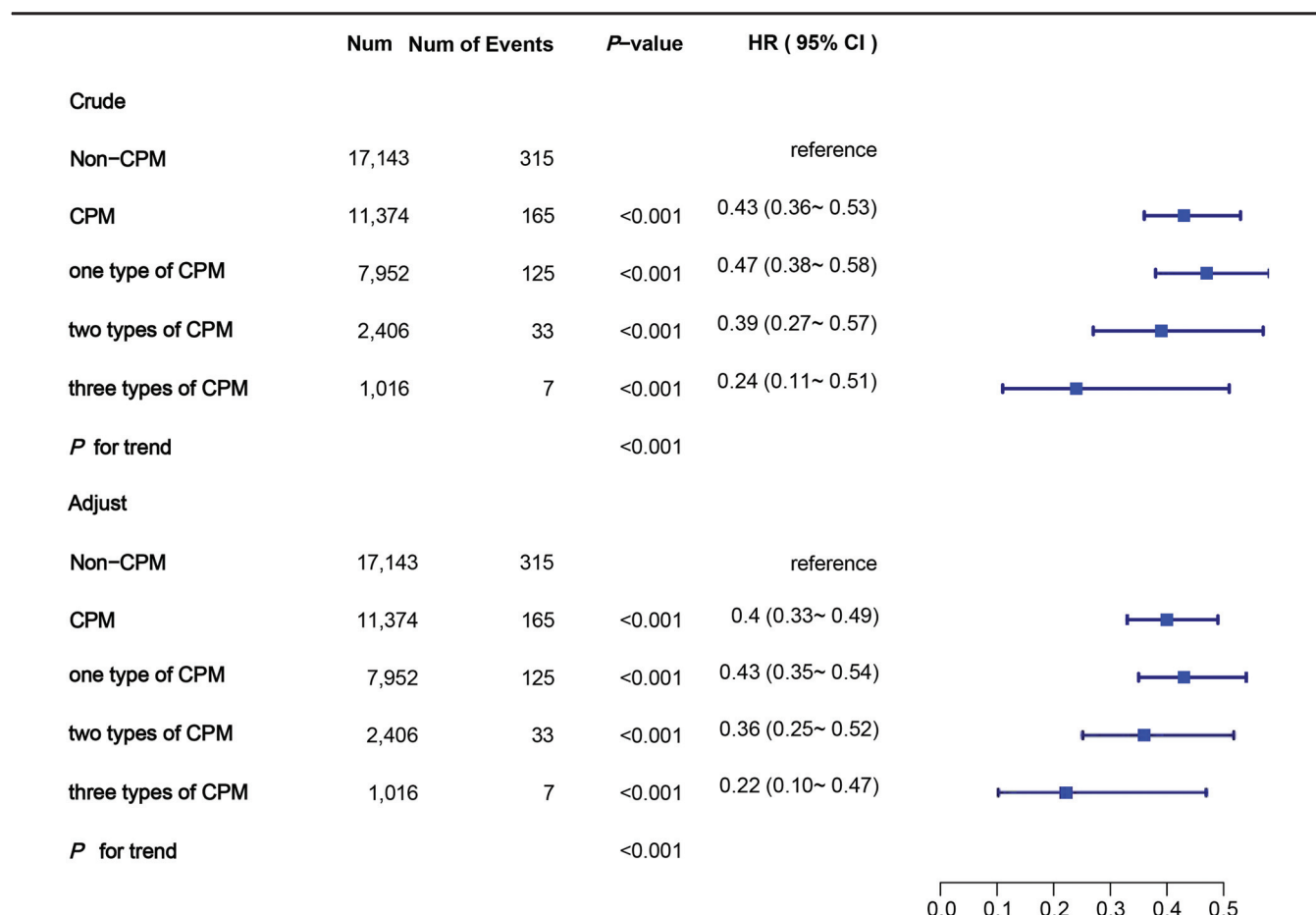


Figure 3. The effect of CPM on the overall incidence of composite MACE in patients with CHD angina pectoris. Results are expressed as hazard ratios (95% confidence intervals). Crude HR represents relative hazard ratio. Adjusted HR represents multivariate-adjusted hazard ratio: sex, age, smoking, drinking, family history of CHD, hypertension, hyperlipidemia, and diabetes are adjusted using a Cox proportional-hazards model. CHD: coronary heart disease; CPM: Chinese patent medicine; MACE: major adverse cardiovascular events; HR: hazard ratio.

the overall incidence of composite MACE, and the effect of CPM in men was better than that in women (Table 2).

Comparison of the overall risks of composite MACE in CHD angina pectoris patients of different ages

Patients with CHD angina pectoris were divided into four subgroups according to their age. The overall risks of composite MACE in the CPM and non-CPM groups at different ages were compared. The Kaplan-Meier curve analysis showed that the overall incidence of composite MACE in the 45 to 54, 55 to 64, and 65 to 75 age groups in the CPM group were lower than those in the non-CPM group. And the 55 to 64 and 65 to 75 years old groups had better results than the 45 to 54 years old groups (Figure 4C–F). The multivariate Cox proportional-hazards model was used to analyze the effect of adjuvant therapy with CPM on the overall incidence of composite MACE in patients with CHD angina pectoris of different age groups, revealing that CPM was an independent protective factor for reducing the overall incidence of composite MACE in patients with CHD angina pectoris in the age groups of 45 to 54 years [adjusted HR=0.32, 95% CI (0.15; 0.68)], 55 to 64 years [adjusted HR=0.30, 95% CI (0.21; 0.42)], and 65 to 75 years [adjusted HR=0.52, 95% CI (0.40; 0.69)]. CPMs have a better therapeutic effect in people aged 55 to 64 years (Table 3).

Supplementary analysis

The results of the sensitivity analysis were consistent with those of the initial analysis. For the sensitivity analysis, we (1) excluded missing values for smoking, drinking, family history of CHD, current antianginal medication, current anticoagulant medication, current antihypertensive medication, current antilipidemic medication, and current antiarrhythmic medication (Supplementary Table 6, <http://links.lww.com/AHM/A15>) and (2) missing values for covariates (Supplementary Table 7, <http://links.lww.com/AHM/A15>).

Discussion

Several studies have demonstrated that adjuvant TCM therapy has significant benefits for patients with cardiovascular diseases^[17], such as heart failure^[18] and myocardial infarction^[19]. There have been reports that TCM can improve the clinical curative effect of patients with angina pectoris^[6]; however, these are mainly based on the outcomes of small-sample RCT studies. The incidence of CHD events has not been reported in any trial. The study is a large-scale, multi-center clinical cohort study to analyze the therapeutic effectiveness of CPM for use as adjuvant therapy for CHD angina pectoris, and we found that CPM adjuvant therapy is a protective factor for reducing the incidence of MACE in patients with angina pectoris.

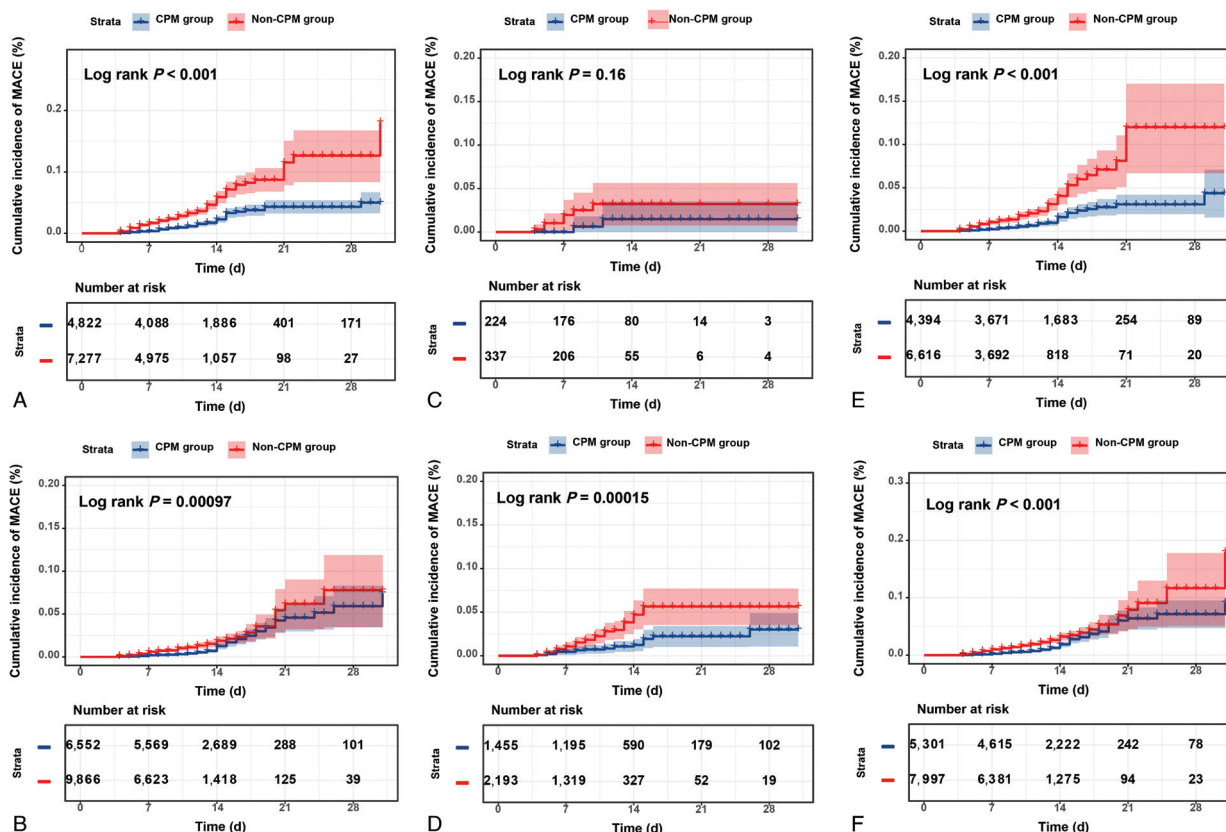


Figure 4. The overall incidence of composite MACE between CPM and non-CPM groups of different sexes and age. (A) Male. (B) Female. (C) 35 to 44 years old. (D) 45 to 54 years old. (E) 55 to 64 years old. (F) 65 to 75 years old. CPM: Chinese patent medicine; MACE: major adverse cardiovascular events.

CPMs are widely used in the clinical treatment of CHD angina pectoris^[20–22], and 18.7% of Chinese patients choose TCM as their favorite therapy^[14]. TCM can decrease the risk of cardiovascular events, improve the conditions of patients, and improve clinical effectiveness^[23–24]. This study involved various CPMs, such as Compound Danshen Dripping Pill (CDDP) and Tongmai Yangxin Pill (TMYX). CDDP (national medicine permission number (NMPN): Z10950111) has pleiotropic effects including improving myocardial function, preventing myocardial ischemia and apoptosis^[25–26]. Several preclinical studies have investigated the mechanism of action of CDDP in the treatment of chronic stable angina; the reported core mechanisms of action include the promotion of coronary microcirculation by preventing microcirculatory disturbances^[27], optimization of myocardial energy by promoting energy production and

protection of mitochondria^[28], and inhibition of platelet activation, and prevention of thrombus formation^[29]. TMYX (NMPN: Z12020589), a commonly used clinical drug, contains eleven Chinese medicinal herbs^[30]. TMYX can efficiently improve the clinical symptoms of patients with coronary arrhythmia^[31] and angina pectoris, as well as augment the plasma concentrations of vascular endothelial growth factor and NO and strengthen vascular endothelial function^[32]. Modern pharmacological research indicates that TMYX can dilate mesenteric arteries precontracted with phenylephrine *in vitro*, and TMYX has anti-inflammatory, antioxidant, and angiogenic effects^[33]. Cai et al.^[34] found that TMYX may improve myocardial dysfunction and amino acid dysfunction and reduce oxidative stress and inflammation.

This study suggests CPM has benefits regardless of the type, sex, and age stratification. The number of

Table 2

The effect of CPM on composite MACE between two groups of different sexes.

Sex	Group	n	No. of events	Crude			Adjust		
				HR	95% CI	P	HR	95% CI	P
Male	Non-CPM	7,277	220	1.00 (Reference)			1.00 (Reference)		
	CPM	4,822	92	0.38	[0.29; 0.48]	<0.001	0.34	[0.26; 0.44]	<0.001
Female	Non-CPM	9,866	95	1.00 (Reference)			1.00 (Reference)		
	CPM	6,552	73	0.60	[0.43; 0.81]	0.001	0.56	[0.41; 0.78]	0.001

CHD: coronary heart disease; CI: confidence interval; CPM: Chinese patent medicine; HR: hazard ratio; MACE: major adverse cardiovascular events.

Results are expressed as hazard ratios (95% confidence intervals). Crude HR represents relative hazard ratio. Adjusted HR represents multivariate-adjusted hazard ratio: sex, age, smoking, drinking, family history of CHD, hypertension, hyperlipidemia, diabetes, current antianginal medication, current anticoagulant medication, current antihypertensive medication, current antilipidemic medication, and current antiarrhythmic medication are adjusted using a Cox proportional-hazards model.

Table 3
The effect of CPM on composite MACE between two groups of different age.

Age	Group	n	No. of events	Crude			Adjust		
				HR	95% CI	P	HR	95% CI	P
35–44	Non-CPM	337	7		1.00 (Reference)			1.00 (Reference)	
	CPM	224	2	0.34	[0.07; 1.63]	0.18	0.31	[0.06; 1.69]	0.18
45–54	Non-CPM	2,193	44		1.00 (Reference)			1.00 (Reference)	
	CPM	1,455	18	0.35	[0.20; 0.62]	<0.001	0.32	[0.15; 0.68]	0.003
55–64	Non-CPM	6,616	119		1.00 (Reference)			1.00 (Reference)	
	CPM	4,394	52	0.33	[0.24; 0.47]	<0.001	0.30	[0.21; 0.42]	<0.001
65–75	Non-CPM	7,997	145		1.00 (Reference)			1.00 (Reference)	
	CPM	5,301	93	0.56	[0.43; 0.73]	<0.001	0.52	[0.40; 0.69]	<0.001

CHD: coronary heart disease; CI: confidence interval; CPM: Chinese patent medicine; HR: hazard ratio; MACE: major adverse cardiovascular events.

Results are expressed as hazard ratios (95% confidence intervals). Crude HR represents relative hazard ratio. Adjusted HR represents multivariate-adjusted hazard ratio: sex, age, smoking, drinking, family history of CHD, hypertension, hyperlipidemia, diabetes, current antianginal medication, current anticoagulant medication, current antihypertensive medication, current antilipidemic medication, and current antiarrhythmic medication are adjusted using a Cox proportional-hazards model.

cardiovascular events in this study decrease with an increase in the types of CPM, and the effect increase with an increase in the types of CPM. The manifestation of CPM effectiveness enriches the types of clinical medication. As the research reports, the effect of drug combination therapy is better than that of a single drug regardless of whether it is TCM or Western medicine^[35]. Sex-related factors can further exacerbate the detrimental effects of established risk factors of CVD^[36–37]. Despite the differences between the CVD risks in males and females, most studies examining the degrees of the effect of each risk factor have customarily focused on male participants^[38]. The prevalence of MACE in the male population is greater than that in the female population in this study, and the therapeutic effects of CPM in the male population are better than those in the female population. Future research can further analyze the characteristics of the male population. Age has different effects on cardiovascular diseases^[39], and the risk of cardiovascular disease increases by 4% with each additional year of biological age^[40–41]. In this study, the prevalence of cardiovascular events also increased with an increase in age; middle-aged people aged 55 to 64 took CPM for better treatment. In optimizing clinical guidance and medication, the use of CPM needs to be appropriately biased towards men and middle-aged people. Patients aged 35 to 44 years may have fewer cardiovascular events, which may lead to unsatisfactory statistical results; however, this does not affect the overall trend. To reduce bias, we use sex, age, smoking, drinking, family history of CHD, and comorbidities as covariates and suggest that the adjusted results do not affect the benefits of CPM in the treatment of CHD angina pectoris.

This study has some limitations. First, the data of this study are retrospective data, and there are differences in baseline characteristics such as family history of CHD, comorbidities, and Western medicine treatment between CPM and non-CPM groups. Although these differences are included as covariates in the statistical analysis, it cannot be fully demonstrated that the effect of bias has been eliminated. Second, the data are collected from the hospital medical record management information system. Different hospitals have different ways of collecting inpatient information, and some data such as smoking, drinking, family history of CHD, and Western medicine treatment may be lost. Therefore, for statistical analysis,

we use multiple imputations to impute missing data. Third, this study only observes the incidence of MACE, the follow-up time is relatively short so death cannot be captured. Therefore, we will design a more rigorous prospective cohort study to further verify the effects of CPM on the survival of patients with angina pectoris. However, our study uses a multicenter cohort and a large sample. Therefore, the results have a high degree of credibility.

Conclusions

Adjuvant treatment with CPM can decrease the incidence of MACE in patients with CHD angina pectoris, especially in men and middle-aged people. Adjuvant treatment with CPM is effective in treating angina pectoris, but this conclusion needs further verification by prospective cohort studies in the future.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Thanks for the conceptualization and methodology of Mingchi Luo and Yijia Liu, the data curation of Rongrong Yang, Yijia Liu, Zhu Li, Xu Wang, Mei Ma, Yuanyuan He, and Tongyao Ni, the investigation of Yijia Liu, Zhu Li, Xu Wang, the writing-original draft preparation and visualization of Yijia Liu, the writing – reviewing and editing of Rongrong Yang and Mingchi Luo.

Ethical approval of studies and informed consent

This study was approved by the Ethics Committee of Tianjin University of Traditional Chinese Medicine (Lot

Number: TJUTCM-EC20190008), and the requirement for informed consent was waived. It has been registered in the Clinical Trials.gov (registration number: NCT04026724) and the Chinese Clinical Trial Registry (registration number: ChiCTR1900024535).

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