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Decreased stroke risk with combined traditional Chinese and western medicine in patients with ischemic heart disease

A real-world evidence

Yu-Chen Cheng, MD[a], Cheng-Nan Lu, MD, MS[a], Wen-Long Hu, MD, MS[a,b,c], Chung Y. Hsu, MD, PhD[d], Yuan-Chih Su[e], Yu-Chiang Hung, MD, PhD[a,*]

Abstract

Both ischemic heart disease (IHD) and stroke are major causes of death worldwide. We investigated the effects of combined Traditional Chinese medicine (TCM) and western medicine (WM) on stroke risk in IHD patients.

Taiwanese patients with IHD were enrolled in the TCM study during their outpatient visit. Stroke events after TCM or non-TCM treatment were examined. Chi-square tests and Student *t*-tests were used to examine differences between patients using and not using TCM. The Cox proportional hazards regression model was used to estimate hazard ratios (HRs). Sex, age, and comorbidities were included in a multivariable Cox model to estimate the adjusted HR (aHR). The survival probability and the probability free of stroke were calculated by the Kaplan–Meier method.

There were 733 IHD patients using TCM and 733 using non-TCM treatment, with the same proportion of sex and age within each cohort. Using single Chinese herb such as Dan Shen, San Qi, or Chuan Xiong would have lower stroke events and lower aHR than non-TCM in IHD patients. There was 0.3-fold lower stroke risk in IHD patients with combination TCM and non-TCM treatment (95% CI = 0.11–0.84, $P = .02$). Moreover, the survival rate was higher ($P < .001$) and the incidence of hemorrhagic stroke was significantly lower ($P = .04$) in IHD patients with TCM treatment.

IHD patients using combined TCM and WM had a higher survival rate and lower risk of new onset stroke, especially hemorrhagic stroke than those who did not use TCM treatment.

Abbreviations: BYHWT = Bu-yang-huan-wu-tang, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, IHD = ischemic heart disease, MI = myocardial infarction, NHIRD = National Health Insurance Research Database, TCM = traditional Chinese medicine, XFZYT = Xue-fu-zhu-yu-tang, ZGCT = Zhi-gan-cao-tang.

Keywords: combined medicine, ischemic heart disease, stroke, traditional Chinese medicine

Editor: Wen-Jun Tu.

Availability of data and materials: The National Health Research Institutes Database (NHIRD) which are managed by National Health Research Institutes in Taiwan. The information in the Longitudinal Health Insurance Database 2000 (LHID 2000) containing one million individuals from the NHIRD was used in this study.

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-212-133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 107-2321-B-039 -004-), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The biostatistics revision was by the Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital and Cheng-Li Lin, the chief biostatistician of Management Office for Health Data (DryLab), Clinical Trial Center (CTC), China Medical University Hospital.

The authors have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, [b] Fooyin University College of Nursing, [c] Kaohsiung Medical University College of Medicine, Kaohsiung, [d] Graduate Institute of Biomedical Sciences, China Medical University, [e] Management Office for Health Data, Clinical Trial Research Center, China Medical University Hospital, Taichung, Taiwan.

[*] Correspondence: Yu-Chiang Hung, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College, No. 123, Dapi Rd., Niaosong Dist., Kaohsiung 83342, Taiwan (e-mail: hungyuchiang@gmail.com).

How to cite this article: Cheng YC, Lu CN, Hu WL, Hsu CY, Su YC, Hung YC. Decreased stroke risk with combined traditional Chinese and western medicine in patients with ischemic heart disease: a real-world evidence. Medicine 2020;99:42(e22654).

Received: 7 April 2020 / Received in final form: 16 August 2020 / Accepted: 8 September 2020

http://dx.doi.org/10.1097/MD.0000000000022654

1. Introduction

Traditional Chinese medicine (TCM) has been treating cardiovascular disease in the Chinese communities for more than 3000 years. Ischemic heart disease (IHD), is also called coronary artery disease, is strongly related to stroke; both stroke and IHD are major causes of death worldwide.[1] However, in several East Asian countries, stroke is more prominent than IHD. East Asian countries have higher mortality rates and incidence rates for stroke, especially hemorrhagic stroke, than do Western counties,[2] likely due to a higher prevalence of hypertension and lower serum total cholesterol levels in Asian countries than in Western countries,[2]

Besides IHD, other comorbidities such as diabetes mellitus (DM), hypertension, hyperlipidemia, and chronic obstructive pulmonary disease (COPD) are also related to stroke. Those comorbidities may affect the prognosis of patients with IHD.

1.1. Diabetes mellitus and stroke

Early onset type 2 DM is associated with a markedly elevated risk of cardiovascular disease,[3] thus increasing the risk of stroke. Individuals with DM have a 2- to 4-fold increase in IHD risk and higher mortality rates than those without DM.[4,5] Furthermore, patients with DM but without a previous myocardial infarction (MI) have a risk of MI as high as patients without DM who have previously had a MI.[6] Further, while intracerebral hemorrhage is most often related to hypertension, patients with DM are more prone to deep subcortical intracerebral hemorrhage.[5] A large scale meta-analysis project, the Asia Pacific Cohort Studies Collaboration, shows that the hazard ratios (HRs) of DM for ischemic stroke and IHD are similar for both Asian and Western countries.[7]

1.2. Hypertension and stroke

Apparent treatment-resistant hypertension is associated with an increased risk for coronary heart disease and all-cause mortality.[8] Hypertension, especially uncontrolled arterial hypertension, is the strongest risk factor for stroke and increases the possibility of a more severe stroke; therefore, it is necessary to effectively control this risk factor to prevent stroke and minimize recurrences.[9]

1.3. Hyperlipidemia and stroke

According to the National Cholesterol Education Panel's Adult Treatment Program-3 guidelines, hyperlipidemia can broadly be classified as elevation of LDL cholesterol(>100 mg/dL), total cholesterol(>200 mg/dL), or triglycerides(>150 mg/dL).[10] Serum total cholesterol level, a measure of hyperlipidemia, is positively correlated with IHD morbidity and mortality in Asian countries.[11] The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification divides patients with ischemic stroke into 5 subgroups:

(1) large-artery atherosclerosis,
(2) cardioembolism,
(3) small-vessel occlusion,
(4) stroke of other determined etiology, and
(5) stroke of undetermined etiology.

Small vessel disease was significantly associated with hyperlipidemia and current smoking.[12,13]

1.4. COPD and stroke

COPD is not only a respiratory disease but is increasingly recognized as a systemic disease with significant clinical extrapulmonary effects.[14] COPD may be complicated by cardiovascular diseases including right ventricular dysfunction, pulmonary hypertension, IHD, dysrhythmias,[15,16] and stroke.[17] There is a strong epidemiological link between IHD and COPD, especially in severe COPD cases[18–20]; in fact, airflow limitations caused by COPD affects almost one-third of IHD patients.[19] The usual treatment for IHD is antithrombotic therapy using various combinations of antiplatelet and anticoagulant drugs.[21] The risk of hemorrhagic stroke is particularly high in patients receiving dual antiplatelet therapy during first year after stroke or a transient ischemic attack.[22]

Since 1995, Traditional Chinese medicine (TCM) has been covered by the National Health Insurance program in Taiwan. Both TCM and WM are covering in NIH.[23] Common single herbs such as Dan Shen (*Salvia miltiorrhiza* Bunge, rhizome) or herbal formulas such as Zhi-gan-cao-tang (ZGCT), San Qi, Xue-fu-zhu-yu-tang (XFZYT), Bu-yang-huan-wu-tang (BYHWT) and Zhi-gan-cao-tang (ZGCT) are used to treat heart disease and cerebrovascular diseases.[24–26] This investigation aimed to provide an analysis of combined TCM and western medicine (WM) therapy effectiveness regarding stroke prevention in IHD patients.

2. Methods and materials

2.1. Data source

The National Health Insurance Research Database (NHIRD) is a secondary database that integrates National Health Insurance data. The NHIRD contains almost all the medical care data of Taiwan residents since 1996 including conventional outpatient visits, inpatient visits, and TCM outpatient visits. Information regarding encrypted identification, visit date, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), prescriptions, and operations are recorded when the patient receives medical treatment. Information in the Longitudinal Health Insurance Database 2000 (LHID 2000) containing one million individuals from the NHIRD was used in this study. This study was approved and waived the need for patient consent by Research Ethics committee China Medical University and Hospital, Taichung, Taiwan (CMUH104-REC2-115(CR-3)).

2.2. Study population

We selected data records for IHD patients (ICD-9CM: 411-414) between the years 2000 and 2010. Individuals younger than 20 years were excluded. The expired date was set as the patients was dead, withdrawn by NHIRD or out of December 31, 2011. IHD patients have all been examined by electrocardiogram and diagnosed by a cardiologist. We classified the IHD patients into 2 groups by receipt of TCM after diagnosis of IHD (TCM user) or no receipt of TCM (non-TCM user). The index date signifying the date of the first TCM outpatient visit was collected for each patient. Frequency matching was used and the ratio was 1:1 for the sex, age, index year, and first IHD diagnosis year.

2.3. Outcome and confounding factors

The incidence of stroke was obtained for IHD patients after receiving TCM treatment; ischemic stroke and hemorrhagic

Table 1

Characteristics of patients with IHD according to TCM use.

	TCM use				
	NO		Yes		
Variable	n	%	N	%	*P*-value*
Sex					.99
Female	330	45.0	330	45.0	
Male	403	55.0	403	55.0	
Age (yrs)					.99
20–39	40	5.46	40	5.46	
40–64	479	65.4	479	65.4	
More than 65	214	29.2	214	29.2	
Mean ± SD	58.1 (12.0)		57.9 (12.1)		.83†
Baseline comorbidity					
Hyperlipidemia	253	34.52	263	35.88	.58
DM	213	29.06	144	19.65	<.001
Hypertension	451	61.53	381	51.98	<.001
COPD	152	20.74	214	29.2	<.001
Chronic kidney disease	40	5.46	20	2.73	<.001
Cirrhosis	193	26.3	243	33.2	<.001
Drug					
Warfarin	30	4.09	44	6	.09
Dipyridamole	247	33.7	282	38.47	.06
Aspirin	480	65.48	522	71.21	.02
Duration between IHD onset and first visit to a TCM clinic, days, median	-		839		

The mean (median) follow-up periods were 6.87 (6.78) years and 4.86 (4.38) years for patients using TCM and not using TCM, respectively.

COPD = Chronic Obstructive Pulmonary Disease, DM = diabetes mellitus, IHD = ischemic heart disease, SD = standard deviation, TCM = traditional Chinese Medicine.

* Chi-Square Test.

† Student *t*-test.

stroke were identified according to ICD-9-CM codes 433-438 and 430-432, respectively. Patients diagnosed with stroke before the index date were excluded. Patients with additional documentation for hyperlipidemia (ICD-9-CM: 272), DM (ICD-9-CM: 250), hypertension (ICD-9-CM: 401-405) and COPD (ICD-9-CM: 490-493, 494, 496), chronic kidney disease (ICD-9-CM: 585), and cirrhosis (ICD-9-CM: 571) were considered to be comorbidities. In order to reduce any concerns surrounding disease misclassification, the criteria for a patient to be included in the main outcome and comorbidity analyses were at least 2 outpatient visits or 1 inpatient visit. WM including warfarin, dipyridamole, and aspirin were also confounding factors included in the statistical evaluation.

2.4. Statistical analysis

Associations of demographic characteristics and confounding factors were examined using Chi-square tests and Student *t*-tests. The Chi-square test was used to test the differences in categorical variables and Student *t*-tests was used to test the differences in continuous variables.

The frequency of TCM prescriptions for IHD patients was calculated along with other information. The event for stroke was calculated in both cohorts. The multivariable Cox proportional hazards regression model was used to assess the stroke risk associated with TCM treatment, and the hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated.

The multivariable model was developed by adjusted for age, sex, hyperlipidemia, DM, hypertension, COPD, chronic kidney disease, and cirrhosis, and warfarin, dipyridamole, and aspirin use. We further analyzed the data to assess the effect of the single Chinese herbal product (CHP) and formula CHPs on the risk of stroke. In addition, we performed Cox proportional hazards regression analysis to measure hazard ratio of stroke among IHD patients by different TCM and non-TCM treatments. The Kaplan-Meier method was used to calculate the survival probability and cumulative incidence of stroke. All analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC). The significance level was set at $P < .05$ in 2-sided tests.

3. Results

The characteristics of the study population are displayed in Table 1. There were 733 patients using TCM and 733 patients who did not, with the same proportion of sex and age in each group. IHD patients over the age of 65 had a greater risk of stroke ($P = .04$; Table 2). There was a significant difference DM, hypertension, COPD, chronic kidney disease, and cirrhosis comorbidities between the groups. ($P < .001$; Table 1) However, only hypertension may affect the risk of stroke ($P = .004$; Table 2). Other comorbidities including hyperlipidemia, DM, COPD, chronic kidney disease, and cirrhosis did not affect the risk of stroke.

Our data suggests that combined TCM and WM use may be likely to reduce the risk of stroke, ischemic stroke, and hemorrhagic stroke. (aHR = 0.85, 0.92, and 0.34 respectively; Table 2) However, only the aHR difference in hemorrhagic stroke between TCM and non-TCM group was nearly significant ($P = .05$; Table 2). We also found the survival probability was higher for patients using TCM than patients not using TCM ($P < .001$; Fig. 1A). The incidence of hemorrhagic stroke was significantly lower in patients using TCM than patients not using TCM ($P = .04$; Fig. 1D).

Table 2

Stroke risk factors among IHD patients.

Variable	Stroke				Ischemic stroke				Hemorrhagic stroke			
	Event no.	aHR	(95% CI)	*P*-value	Event no.	aHR	(95% CI)	*P* value	Event no.	aHR	(95% CI)	*P*-value
TCM												
No	86	1	(Reference)		76	1	(Reference)		10	1	(Reference)	
Yes	109	0.85	(0.63–1.14)	.28	104	0.92	(0.68–1.25)	.59	5	0.34	(0.11–1.02)	.05
Sex												
Female	98	1	(reference)		92	1	(Reference)		6	1	(Reference)	
Male	97	0.89	(0.67–1.19)	.44	88	0.86	(0.64–1.16)	.32	9	1.46	(0.51–4.22)	.48
Age group (yrs)												
20–39	3	1	(REFERENCE)		3	1	(Reference)		0			
40–64	96	1.65	(0.52–5.29)	.40	88	1.46	(0.46–4.7)	.52	8			
More than 65	96	3.47	(1.07–11.22)	.04	89	3.05	(0.94–9.89)	.06	7			
Baseline comorbidity (Yes vs No)												
Hyperlipidemia	71	0.79	(0.58–1.08)	.14	66	0.79	(0.57–1.09)	.16	5	0.8	(0.26–2.48)	.70
DM	53	1.11	(0.79–1.57)	.53	50	1.15	(0.81–1.63)	.44	3	0.81	(0.21–3.12)	.76
Hypertension	139	1.63	(1.17–2.26)	.004	129	1.66	(1.18–2.35)	.004	10	1.3	(0.42–3.98)	.65
COPD	63	1.25	(0.91–1.71)	.16	61	1.32	(0.96–1.82)	.09	2	0.47	(0.1–2.22)	.34
CKD	6	0.74	(0.32, 1.69)	.47		0.65	(0.26,1 .61)	.35				
Cirrhosis	67	1.21	(0.88, 1.65)	.25		1.19	(0.86, 1.65)	.29				
Drug (Yes vs No)												
Warfarin	24	2	(1.29–3.09)	.002	20	1.76	(1.1–2.83)	.02	4	5.72	(1.71–19.18)	.005
Dipyridamole	116	1.91	(1.42–2.56)	<.001	108	1.94	(1.42–2.63)	<.001	8	1.78	(0.63–5.05)	.28
Aspirin	173	2.8	(1.78–4.41)	<.001	160	2.88	(1.79–4.63)	<.001	13	1.97	(0.42–9.27)	.39

aHR represents the hazard ratio adjusted for age, sex, hyperlipidemia, DM, hypertension, COPD, chronic kidney disease, and cirrhosis, and warfarin, dipyridamole, and aspirin use.
aHR = adjusted hazard ratio, CI = confidence interval, CKD = chronic kidney disease, COPD = Chronic Obstructive Pulmonary Disease, DM = diabetes mellitus, TCM = traditional Chinese Medicine.

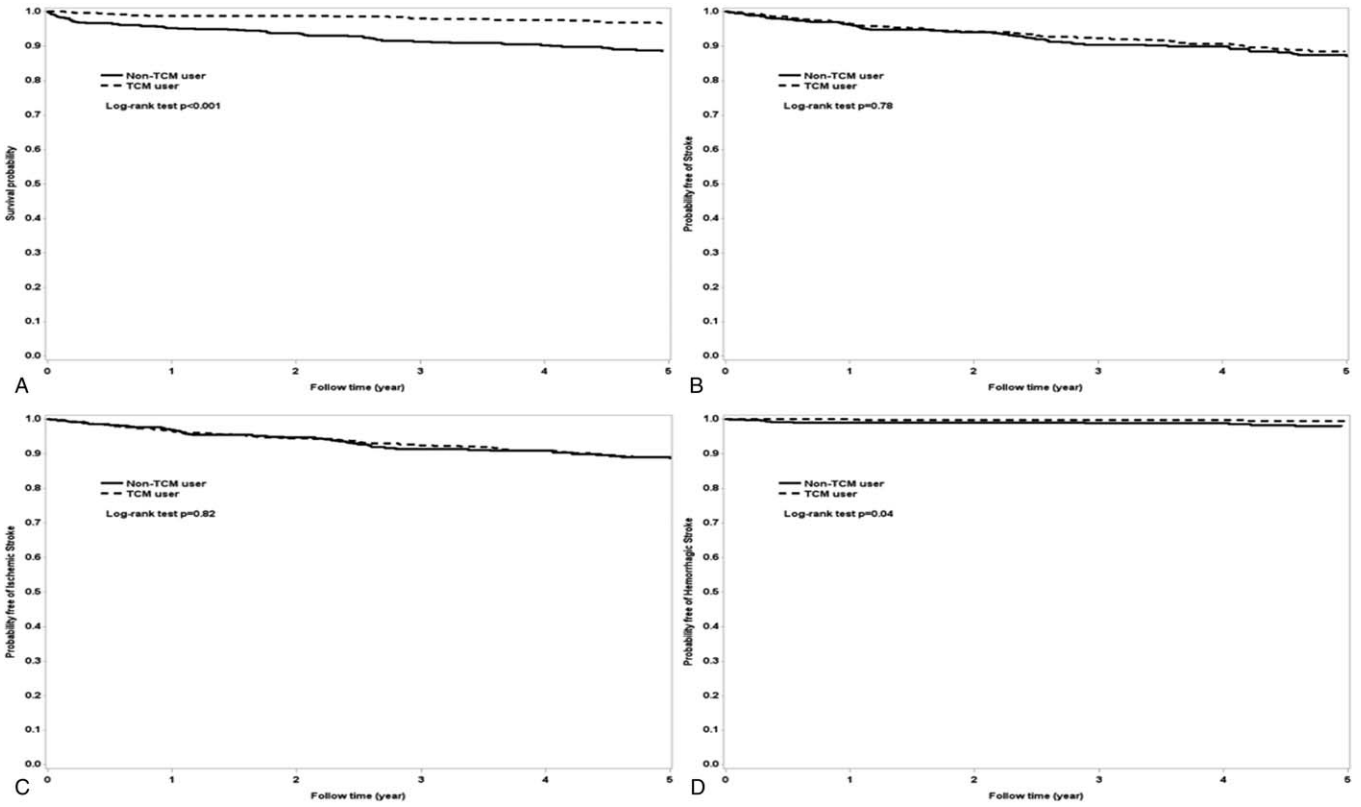

Figure 1. Kaplan-Meier analysis of estimating (A) survival probability; (B) probability free of stroke; (C) probability free of ischemic stroke; (D) probability free of hemorrhagic stroke between ischemic heart disease patients using TCM and those not using TCM. TCM = traditional Chinese Medicine.

Table 3

Hazard Ratios and 95% confidence intervals of stroke associated with TCM use among IHD patients.

		Stroke			Ischemic stroke			Hemorrhagic stroke		
			Hazard Ratio (95% CI)			Hazard Ratio (95% CI)			Hazard Ratio (95% CI)	
TCM prescription	N	Event no.	Crude*	Adjusted†	Event no.	Crude*	Adjusted†	Event no.	Crude*	Adjusted†
Patients not using TCM	733	86	1.00 (reference)	1.00 (reference)	76	1.00 (reference)	1.00 (reference)	10	1.00 (reference)	1.00 (reference)
Single CHPs										
Dan Shen	244	33	0.83 (0.55–1.24)	0.67 (0.44–1.02)	32	0.91 (0.60–1.37)	0.74 (0.48–1.15)	1	0.22 (0.03–1.75)	0.18 (0.02–1.47)
San Qi	90	13	1.0 (0.56–1.79)	0.87 (0.48–1.58)	12	1.04 (0.57–1.91)	0.88 (0.47–1.64)	1	0.66 (0.09–5.18)	0.71 (0.09–5.63)
Chuan Xiong	54	7	0.87 (0.40–1.89)	0.52 (0.23–1.19)	7	0.98 (0.45–2.13)	0.58 (0.25–1.35)	0		
Formula CHPs										
XFZYT	197	36	1.14 (0.77–1.68)	1.03 (0.69–1.54)	36	1.28 (0.86–1.90)	1.13 (0.75–1.69)	0		
BYHWT	30	6	1.30 (0.57–2.98)	1.23 (0.53–2.86)	5	1.22 (0.50–3.02)	1.21 (0.48–3.05)	1	1.94 (0.25–15.1)	1.89 (0.21–16.7)
ZGCT	196	27	0.89 (0.57–1.37)	0.69 (0.44–1.1)	26	0.96 (0.61–1.5)	0.76 (0.47–1.23)	1	0.30 (0.04–2.32)	0.23 (0.03–1.97)

Crude HR* represents relative hazard ratio; Adjusted HR† represented the hazard ratio mutually adjusted for age, sex, hyperlipidemia, DM, hypertension, COPD, chronic kidney disease and cirrhosis. *$P < .05$, **$P < .01$, ***$P < .001$.

BYHWT = Bu-yang-huan-wu-tang, CHP = Chinese herbal product, TCM = traditional Chinese Medicine, XFZYT = Xue-fu-zhu-yu-tang, ZGCT = Zhi-gan-cao-tang.

TCM consists of either single Chinese herbal products (CHPs) or formula CHPs. We compared the hazard ratios of stroke among IHD patients associated with the commonest single CHPs such as Dan Shen, San Qi, Chuan Xiong or formula CHPs such as Xue-fu-zhu-yu-tang, Bu-yang-huan-wu-tang, Zhi-gan-cao-tang, respectively. Neither common single CHPs nor formula CHPs demonstrated a significantly effective reduction in the risk of stroke among IHD patients (Table 3). IHD patients with combination TCM and WM treatment would have a 0.3-fold lower risk of stroke risk (95% CI = 0.11–0.84, $P = .02$; Table 4). The possible mechanisms of frequently used CHPs (single and formula) for IHD and stroke are presented in Table 5.

4. Discussion

This population-based study using the health insurance database can be almost regarded as the real-world evidence in Taiwan. Through this nationwide cohort analysis, we showed that combined TCM and WM may decrease the risk of stroke and increase the survival rate in IHD patients.

According to this analysis and previous studies,[25,27,28] single and formula CHPs including Dan Shen, San Qi, Chuan Xiong, XFZYT, BYHWT, and ZGCT can be used to treat IHD and stroke. Dan Shen, a common CHP used to improve blood stasis in IHD patients, has antioxidant effects, inhibits smooth-muscle-cell proliferation, and protects against vascular atherosclerotic lesions by suppressing reactive oxygen species via the PKC/p44/42 MAPK-dependent pathway.[29,30] Salvianolic acid is an active polyphenol component in Dan Shen (*Salvia miltiorrhiza*) that protects against ischemia/reperfusion injury; neuroprotection is dependent on mitochondrial connexin-43 via the PI3K/Akt pathway.[31] San Qi could promote stroke recovery by influencing expression of Nogo-A, NgR, and p75NGF, in vitro and in vivo[37] and provide neuroprotection by increasing P-Akt and P-mTOR expression while reducing P-PTEN and caspase-3 expression in ischemic stroke cases.[38] The other Chuan Xiong would reduce cerebral infarct area and neurological deficit-scores partially attributed to the inhibition of superoxide radicals and expression of ICAM-1 and NF-κB in transient middle cerebral artery occlusion rats.[40] BYHWT has been used to treat and prevent ischemic cardio-cerebral vascular diseases and stroke-induced disabilities for thousands of years. Additionally, ZGCT has been frequently used for generations to treat heart disease, especially arrhythmia, in patients with a knotted irregular pulse and severe palpitations.[32] ZGCT enhances *Qi*, nourishes *Yin*, tonifies *Yang*, nourishes the blood and reduces palpitations.

The survival rate during follow-up was higher in patients using TCM, and the incidence of hemorrhagic stroke was lower. Our results support the findings of a meta-analysis of 22 randomized-controlled trials on ischemic stroke and four on hemorrhagic stroke reporting the benefits of TCM and highlighting improvements in neurological function and overall therapeutic efficacy in poststroke patients.[33]

Table 4

The risk of stroke in IHD patients with different prescription combination.

Combination of prescription		Stroke				Ischemic stroke				Hemorrhagic stroke			
TCM prescription	Non-TCM prescription	Event no.	aHR	(95% CI)	*P* value	Event no.	aHR	(95% CI)	*P* value	Event no.	aHR	(95% CI)	*P* value
No	No	14	1	(reference)		12	1	(reference)		2	1	(reference)	
Yes	No	2	0.33	(0.08–1.47)	.16	2	0.40	(0.09–1.78)	.23	0	—	—	
No	Yes	123	0.37	(0.13–1.01)	.05	112	0.42	(0.15–1.17)	.10	13	0.45	(0.03–6.30)	.55
Yes	Yes	56	0.30	(0.11–0.84)	.02	54	0.36	(0.12–1.03)	.06	3	0.19	(0.01–3.26)	.25

The TCM prescription included Dan Shen, San Qi, Chuan Xiong, Xue-fu-zhu-yu-tang, Bu-yang-huan-wu-tang and Zhi-gan-cao-tang. The non-TCM prescription included warfarin, dipyridamole, and aspirin. aHR represented the hazard ratio: mutually adjusted for age, gender, hyperlipidemia DM, hypertension, COPD, chronic kidney disease, cirrhosis, warfarin, dipyridamole, and aspirin in Cox proportional hazard regression.

aHR = adjusted hazard ratio, CI = confidence interval, TCM = traditional Chinese Medicine.

Table 5

Possible mechanisms of frequently used CHPs for IHD.

Single or Formula CHPs	Known active herb constituents and formula ingredients	Possible pharmacological effects on IHD and stroke
Bu-yang-huan-wu-tang (BYHWT)	(Huang Qi) *Astragalus propinquus* Schischkin, root[†] (Dang Gui) *Angelica sinensis* (Oliv.) Diels, root (Chi Shao Yao) *Paeonia lactiflora* Pall., root (Di Long) Pheretima aspergillum(E. Perrier) (Chuan Xiong) *Ligusticum striatum* DC., rhizom (Tao Ren) *Prunus persica* (L.) Batsch, seed (Hong Hua) *Carthamus tinctorius* L., flower	Enhances blood circulation and activates energy (*Qi*) flow through energy meridians while providing neuroprotective effects for conditions such as brain ischemia, stroke-induced disability, and cerebral ischemia-reperfusion injury[39,40] Improvement in stroke symptoms and extended lifespan, primarily by regulating inflammation, apoptosis, angiogenesis, and blood coagulation achieved via up-regulation and mediating neurogenesis and nervous system development[41] Inhibits C-reactive protein and CD40 gene and regulates endothelium-derived vasoactive factors in coronary heart disease cases with *Qi* deficiency and blood stasis syndrome in rats[42]
Xue-fu-zhu-yu-tang (XFZYT)	(Dang Gui) Angelica sinensis (Oliv.) Diels, root (Sheng Di Huang) *Rehmannia glutinosa* (Gaertn.) DC., root (Tao Ren) *Prunus persica* (L.) Batsch, seed (Hong Hua) *Carthamus tinctorius* L., flower (Zhi Ke) *Citrus × aurantium* L., ripe fruit (Chi Shao Yao) *Paeonia lactiflora* Pall., root (Chai Hu) *Bupleurum chinense* DC., root (Gan Cao) Glycyrrhiza uralensis Fisch., root (Jie Geng) *Platycodon grandiflorus* (Jacq.) A.DC., root (Chuan Xiong) *Ligusticum striatum* DC., rhizome (Niu Xi) *Cyathula officinalis* K.C.Kuan, root	Alleviates coronary artery diseases,[43] thromboembolic stroke, atherosclerosis, and hyperlipidemia[44] caused by blood and *Qi* stasis Shows neuroprotective effects by inhibiting HIF-1 α and TNF-α, followed by the inhibition of inflammatory responses (ie, iNOS) and apoptosis (active caspase-3) Lowers serum total-triglyceride concentrations strongly decreases the TXA2/PGI2 ratio and attenuates production of pro-inflammatory cytokines in high-cholesterol-fed rats[45]
Zhi-gan-cao-tang (ZGCT)	(Zhi Gan Cao) Glycyrrhiza uralensis Fisch., root and rhizome, honeyed (Ren Shen) Panax ginseng C.A.Mey., root (Gui Zhi) Cinnamomum cassia (L.) J.Presl, twig (Sheng Jiang) Zingiber officinale Roscoe, fresh rhizome (E Jiao) Equus asinus L., skin (Sheng Di Huang) Rehmannia glutinosa (Gaertn.) DC., root (Mai Dong) Ophiopogon japonicus (Thunb.) Ker Gawl., rhizome (Huo Ma Ren) Cannabis sativa L., seed (Da Zao) Ziziphus jujuba Mill., fruit	Improves heart *Qi* deficiency,[25] warms heart *Yang*, improves blood circulation, and removes blood stasis[46] Blocks different ion channels to shorten the action potential duration of ventricular muscle cells and increases self-discipline[47]
Dan Shen	*Salvia miltiorrhiza* Bunge, rhizome	Shows anti-atherosclerotic, anti-cardiac hypertrophic, anti-oxidant, and anti-arrhythmic effects by promoting blood circulation and provides relief from blood stasis Improves microcirculation, causes coronary vasodilatation, suppresses the formation of thromboxane, inhibits platelet adhesion and aggregation, and protects against myocardial ischemia[48,49]
San Qi	*Panax notoginseng* (Burkill) F.H.Chen, root	Promotes stroke recovery by influencing expression of Nogo-A, NgR, and p75NGF, in vitro and in vivo[50] Provides neuroprotection by increasing P-Akt and P-mTOR expression while reducing P-PTEN and caspase-3 expression in ischemic stroke cases[51]; reduces infarction volume and alleviates neurological deficits caused by cerebral ischemia-reperfusion[52]
Chuan Xiong	*Ligusticum striatum* DC., rhizome	Reductions in cerebral infarct area and neurological deficit-scores were at least partially attributed to the inhibition of superoxide radicals and expression of ICAM-1 and NF-κB in transient middle cerebral artery occlusion rats[53]

CHP = Chinese herbal product, IHD = ischemic heart disease, NGF = nerve growth factor, NgR = Nogo receptor, TCM = traditional Chinese medicine.

[*] All botanical plant names are based on "The Plant List (http://www.theplantlist.org/)."

We did not find differences among patients using single or formula CHPs; this may due to variations in TCM prescriptions since adjustments are made during each visit according to the patient's chief complaints which affects the different TCM syndrome. Nevertheless, a randomized, double-blind, parallel-controlled clinical trial revealed similarities between prescriptions and TCM syndrome; ischemic stroke analyses showed complete (series of formulas) and incomplete (only one formula) prescriptions and TCM syndromes have similar effects on the central clinical manifestations of ischemic stroke, such as neurological deficits and difficulty performing activities in daily living. However, there were significant

differences in individual dysfunctions, such as subjective symptoms.[34]

Our results revealed there is a higher risk of stroke in IHD patients over 65 years old. A global study reported that the mean age of people with incident hemorrhagic stroke was 69.1 ± 0.15 years in high-income countries and 63.8 ± 0.13 years in low- and middle-income countries.[35] In other studies of Chinese epidemiology, stroke incidence increased with age. The highest rates were in people aged over 75 years, where the incidence rate was 30 times that of individuals aged 35 to 44 years.[36] These results are consistent with our finding. In addition, there were some significant differences between 2 groups in baseline comorbidities. It might mean the patients with COPD preferred to use TCM, while the patients with DM and hypertension were not disposed to receive TCM. Besides, patients received aspirin in TCM group might have more will to accept TCM treatment. Aspirin was one of the first-choice drugs not only for IHD but also for ischemic stroke. It was interesting that in our study, patients using TCM might have the lower incidence of hemorrhage stroke. Comparing the most common used single and formula CHPs, most of prescriptions are promoting blood circulation and relieving blood stasis. This result might give us other hint that combining of TCM and anticoagulation/antiplatelet agents might not increase the risk of hemorrhage. The mechanism was unclear and it might need more studies to prove it.

There were some several limitations in this study. First, the patients not using TCM may have received other complementary therapies during the study. Second, The TCM data from the NHIRD database was confined to CHPs, and herbal decoctions were not recorded. Third, lifestyle-related information such as data on alcohol use, cigarette smoking, weight, or socioeconomic status was not available. Forth, novel oral anticoagulants for stroke prevention such as dabigatran, rivaroxaban, and apixaban were not included in our analysis. Finally, the study cases were selected according to ICD-9 codes, potentially causing a misclassification bias despite the ability of the auditing mechanism used by the National Health Insurance Administration to minimize diagnostic uncertainty and misclassification.[37] Recently, linking across the NHIRD and other health-related databases for data management and analyses are trying to execute.[38] This might decrease the coding and data inaccuracy rate in the future.

5. Summary/Conclusions

IHD patients using combined TCM and WM had a higher survival rate and a lower risk of new onset stroke, especially hemorrhagic stroke than those who did not use TCM treatment. Therefore, combination of TCM and WM may prevent stroke in IHD patients.

Author contributions

Conceptualization: Wen-Long Hu, Yu-Chiang Hung.
Data curation: Chung Y. Hsu, Yuan-Chih Su.
Formal analysis: Yuan-Chih Su.
Investigation: Yu-Chen Cheng, Wen-Long Hu, Yu-Chiang Hung.
Methodology: Wen-Long Hu, Chung Y. Hsu, Yuan-Chih Su, Yu-Chiang Hung.
Project administration: Wen-Long Hu, Chung Y. Hsu, Yu-Chiang Hung.
Supervision: Chung Y. Hsu, Yu-Chiang Hung.
Validation: Cheng-Nan Lu, Wen-Long Hu, Yu-Chiang Hung.
Visualization: Cheng-Nan Lu, Wen-Long Hu, Yu-Chiang Hung.
Writing – original draft: Yu-Chen Cheng, Yuan-Chih Su, Yu-Chiang Hung.
Writing – review & editing: Cheng-Nan Lu, Wen-Long Hu, Yu-Chiang Hung.

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