

Association of Traditional Chinese Medicine Therapy and the Risk of Vascular Complications in Patients With Type II Diabetes Mellitus

A Nationwide, Retrospective, Taiwanese-Registry, Cohort Study

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Abstract: With an increasing use of traditional Chinese medicine (TCM) in type 2 diabetes mellitus (T2DM), evidence of long-term benefit with adjunctive TCM treatment is limited. This study investigated whether the concurrent TCM treatment reduces the risk of vascular complications in T2DM patients by using a large population from National Health Insurance Research Database (NHIRD).

We identified 33,457 adult patients with newly diagnosed T2DM using anti-diabetic agents from a random sample of one million beneficiaries in the NHIRD between January 1, 2000 and December 31, 2011. We recruited 1049 TCM users (received TCM over 30 days with a diagnosis of T2DM) and randomly selected 4092 controls as the non-TCM cohort at a ratio of 1:4 frequency-matched by age, sex, hypertension, hyperlipidemia, and index year. We investigated the prescription pattern of TCM and conducted a Cox proportional hazards regression to calculate the hazard ratios (HRs) of stroke, chronic kidney diseases (CKD), and diabetic foot between the 2 cohorts.

In the TCM cohort, the prescription pattern of TCM was different between insulin and noninsulin patients. The most common herbs were *Dan-Shen (Radix Salviae Miltiorrhizae)* in noninsulin group and *Da-Huang (Radix et Rhizoma Rhei)* in insulin group. The most common formulae were *Liu-Wei-Di-Huang-Wan* in noninsulin group and *Yu-Quan-Wan* in insulin group. Although no significant reduction in the hazard ratio of CKD and diabetic foot, the incidence rate of stroke was 7.19 per 1000 person-years in the TCM cohort and 10.66 per 1000 person-years in the control cohort, respectively. After adjustment of age, sex, hypertension, hyperlipidemia, and antidiabetes agent use (including sulfonylureas, α -glucosidase, metformin, meglitinide, thiazolidinediones, and insulin),

TCM cohorts were found to have a 33% decreased risk of stroke (95% CI = 0.46–0.97; $P < 0.05$).

This population-based retrospective study showed that the complementary TCM therapy might associate with the decreased risk of stroke in T2DM, suggesting TCM as an adjunctive therapy for T2DM to prevent subsequent stroke.

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Abbreviations: CHPs = Chinese herbal products, CI = confidence interval, CKD = chronic kidney diseases, EA = electroacupuncture, FFA = free fatty acid, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, IR = incidence rate, IRR = incidence rate ratio, LHID = Longitudinal Health Insurance Database, *LWDHW* = *Liu-Wei-Di-Huang-Wan*, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, SD = standard deviation, T2DM = type 2 diabetes mellitus, TCM = traditional Chinese medicine.

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) has increased steadily worldwide, estimated to be 2.8% in 2000 and predicted to be 4.4% in 2030.¹ Patients with diabetes are at risk of developing a spectrum of vascular complications, such as stroke, nephropathy, retinopathy, and foot ulcers. The current treatment for vascular complications is glycemic control. However, most patients who have T2DM develop vascular complications despite intensive glycemic control with a variety of antidiabetes medications and disease monitoring.² Thus T2DM continues to be an important public health concern because of substantial morbidity and mortality as well as long-term complications. With no specific treatments for vascular complications other than glucose control, alternative therapies have become increasingly popular as adjunctive treatments.

Traditional Chinese medicine (TCM) is a form of complementary and alternative medicine that has been widely applied for centuries in Asian countries. In Taiwan, TCM is a widely used form of medical treatment as well as Western medicine.^{3–6} Both forms of treatment are covered by National Health Insurance (NHI), which is a government-run, single-payer program that covers more than 99% of Taiwanese citizens and over 93% of Taiwanese healthcare institutes.⁷ TCM therapy has gained popularity as a complementary and alternative therapy for diabetes and its complications in Taiwan. Although previous studies implied potential hypoglycemic effects of TCM,^{8,9} evidence of benefit with long-term adjunctive TCM treatment is limited. Chronic subclinical inflammation is associated with

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insulin resistance and many TCM herbs have been reported to exert a hypoglycemic effect via their anti-inflammatory mechanism. In addition to blood glucose and glycosylated hemoglobin (HbA1c), the incidence of vascular complications could be a possible outcome measurement for the long-term TCM treatment effect.

To fill in the gap between TCM therapy and its long-term benefit on T2D, we conducted a large-scale clinical analysis of TCM on vascular complications in T2DM patients. By using a large population-based database from the NHI research database, we investigated whether the integration of TCM and Western medicine reduced the risk of vascular complications among T2DM patients.

METHODS

Data Source

This study was designed as a population-based cohort study analyzing from a sample of 1 million subjects (Longitudinal Health Insurance Database 2000, LHID2000) which was randomly selected from the 23 million beneficiaries of the National Health Insurance Research Database (NHIRD) in Taiwan to determine the risk of complications while combining TCM treatment with Western medicine. This National Health Insurance program was established on March 1, 1995 by Taiwan's Bureau of National Health Insurance (NHI) and it covers over 22.60 million people in Taiwan (total population = 22.96 million).⁷ The LHID2000 comprises medical records such as inpatient and outpatient claims, administered treatments, and personal information such as sex, date of birth, and the date that patients enrolled in the NHI program. The identification of insurants in the LHID2000 was encrypted

before being sent to the researchers. We defined disease on the basis of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

Study Subjects

The subjects were selected from the random 1 million individuals as follows (Figure 1). We considered patients to be T2DM sufferers if antidiabetic medication had been prescribed. First, we included patients who were newly diagnosed T2DM (ICD-9-CM 250.00, 250.000, and 250.02) and treated with antidiabetic agents between January 1, 2000 and December 31, 2011 ($n = 33,457$). Patients using TCM over 30 days with a diagnosis of T2DM were defined as TCM users, whereas those treated for less than 30 days were considered as non-TCM users. Their use of antidiabetic agent, including sulfonylureas, α -glucosidase, metformin, meglitinide, thiazolidinediones, and insulin, was also analyzed. The index date in TCM users was defined the 30th day under TCM treatment. We excluded patients with a history of stroke (ICD-9-CM 430–438), chronic kidney diseases (CKD) (ICD-9-CM 585, 250.40 or 250.42), diabetic foot (ICD-9-CM 682.7, 682.9, 444.22, 728.86, 707.0–707.7 or operation for amputation, debridement, or osteotomy), trauma, or fracture within 180 days before the date of index date, leaving 1049 diabetic patients. To assemble a comparison cohort, we randomly selected controls who were matched with the study cohort at a ratio of 1:4 on frequency of age, sex, hypertension, hyperlipidemia, and index year as the comparison cohort, using the same exclusion criteria during the same period. Finally, we selected 1049 patients as the TCM-combined cohort (mean age = 53.4 years, SD = 11.1 years). The 4092 controls (mean age = 53.7 years, SD = 10.7 years) comprised patients who received TCM <30 days following their T2DM diagnosis

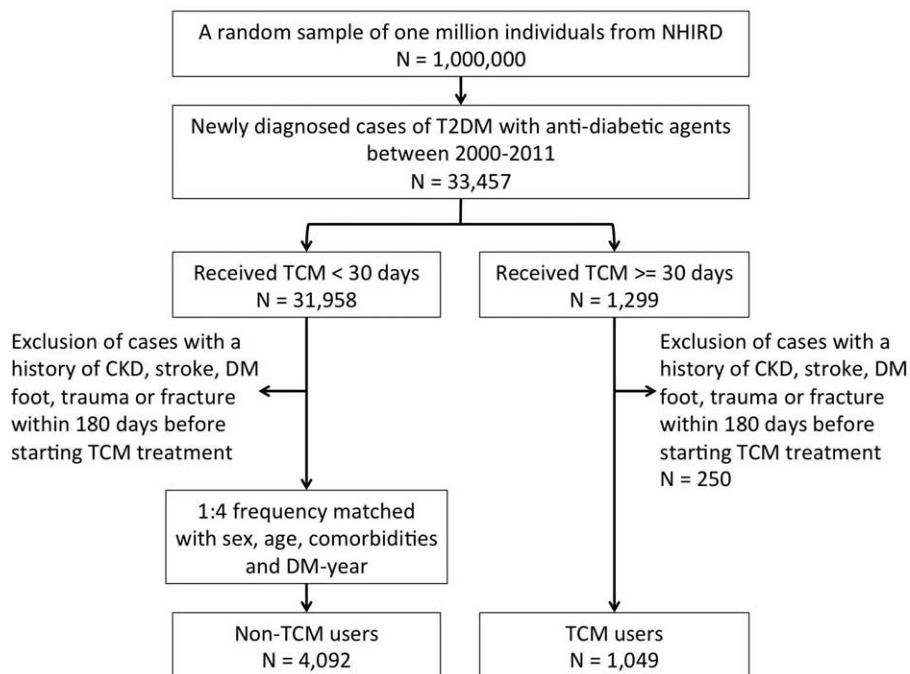


FIGURE 1. Flow recruitment chart of newly diagnosed type 2 diabetes mellitus patients from a random sample of 1 million individuals from the National Health Insurance Research Database in Taiwan. NHIRD = National Health Insurance Research Database; T2DM = type 2 diabetes mellitus; TCM = traditional Chinese medicine.

and their index dates were randomly assigned as TCM users. The Institutional Review Board of the China Medical University and Hospital approved this study (CMU-REC-101–102).

Endpoint

The data were examined from the index date until the endpoint, which was based on whichever of the following occurred first: the date a patient was diagnosed of stroke (ICD-9-CM 430–438), CKD (ICD-9-CM 585, 250.40, or 250.42), or diabetic foot (ICD-9-CM 682.7, 682.9, 444.22, 728.86, 707.0–707.7 or operation for amputation, debridement, or ostectomy); the date a patient withdrew from the NHI program; and the end of 2011.

Statistical Analyses

To test the differences in distribution between the 2 cohorts, we used the χ^2 test for the categorical variable and the *t* test for continuous variable. The χ^2 tests were carried out to examine the differences in the distribution of demographic factors and comorbidities between TCM users (using TCM and Western medicine) and non-TCM users (using Western medicine only). To understand the utility of different TCM therapies in T2DM patients, we displayed the frequency distribution. The most frequently prescribed single herbs and herbal formulae were described. For subjects who did not receive insulin at baseline in both groups, we also examine the incidence of insulin use in the follow-up duration. We counted person-years on the basis of the index date to the endpoint for each patient. The incidence of stroke, CKD, and diabetic foot in 2 cohorts was calculated. To compare the TCM and non-TCM cohorts, we estimated the incidence rate ratio and 95% confidence intervals (CIs) of complications by using Poisson regression. The multivariate model was controlled using age, sex, hypertension, hyperlipidemia, and anti-diabetes agent use (including sulfonylureas, α -glucosidase, metformin, meglitinide, thiazolidinediones, and insulin) by Cox’s proportional hazard regression.

RESULTS

The TCM and non-TCM cohorts comprised data for 1049 and 4092 patients, respectively. Details of the demographic distribution and comorbidities of 2 groups are presented in Table 1. There are more men than women in both groups. Because we matched the distribution of age stratum (every 5 years), sex, and comorbidities (including hypertension and hyperlipidemia), there was no significant difference in those variables. Regarding Western medicine used at baseline, TCM users were more likely to receive α -glucosidase, meglitinide, and thiazolidinediones. To understand the utility of different TCM therapies in T2DM patients, we displayed the frequency distribution. Among total 121,096 TCM clinical visits in T2DM patients, the most frequent TCM therapy was Chinese herbal products (CHPs) (78.2%), followed by acupuncture (12.6%) and manipulative therapy (6.61%). There are few TCM users who use 2 or more different TCM therapies.

To investigate the prescription pattern for TCM users, we divided the TCM cohort into 2 groups, 1 with insulin use and 1 without. In the group without insulin use, the most common single herbs were *Dan-Shen*, *Tian-Hua-Fen*, and *Huang-Qi* (Table 2), and the most common herbal formulae were *Liu-Wei-Di-Huang-Wan*, *Bai-Hu-Jia-Ren-Sheng-Tang*, and *Yu-Quan-Wan* (Table 3). In the group receiving insulin treatment, the most common single herbs were *Da-Huang*, *Tian-Hua-Fen*, *Dan-Shen*, and the most

TABLE 1. Demographic Characteristics Between Type 2 Diabetes Users With and Without Traditional Chinese Medicine

	TCM Users N = 1049		Non-TCM Users N = 4092		P Value
	n	%	n	%	
Men	591	56.3	2318	56.7	0.86
Average age, yr (SD)	53.4 (11.1)		53.7 (10.7)		0.49
Comorbidities					
Hypertension	493	47.0	1935	47.3	0.87
Hyperlipidemia	592	56.4	2303	56.3	0.93
Anti-diabetes agent					
Sulfonylureas	744	70.9	2847	69.6	0.40
α -glucosidase	151	14.4	460	11.2	0.005
Metformin	751	71.6	2831	69.2	0.13
Meglitinide	124	11.8	328	8.02	0.0001
Thiazolidinediones	150	14.3	463	11.3	0.008
Insulin use	175	16.7	616	15.1	0.19

SD = standard deviation; TCM = traditional Chinese medicine.

common herbal formulae were *Yu-Quan-Wan*, *Liu-Wei-Di-Huang-Wan*, and *Zhi-Bo-Di-Huang-Wan*.

We also examine whether adjunctive TCM could decrease the incidence of subsequent insulin use. Among 3476 non-TCM users and 874 TCM users who did not receive insulin at baseline, there are 647 and 177 patients who use insulin in the following of the study, respectively. In patients who did not receive insulin at baseline, the incidence of subsequent insulin use in TCM and non-TCM cohorts was 50.03 and 46.24 per 1000 person-years, respectively. The risk for subsequent insulin use was not significantly different between 2 cohorts (95% CI = 0.91–1.27).

Comparing TCM and non-TCM groups, we examine the incidence of 3 vascular complications (stroke, CKD, and diabetic foot) to evaluate the long-term effect of adjunctive TCM treatment (Table 4). During the follow-up, the incidence of CKD and diabetic foot between 2 groups did not achieve statistical significance. However, 33 TCM patients and 186 non-TCM patients had stroke, and the incidence rates of stroke among the TCM and control cohorts were 7.19 and 10.66 per 1000 person-years, respectively. Compared with the non-TCM cohort, patients who received adjunctive TCM to treat their T2DM exhibited a 33% lower risk for stroke (95% CI = 0.46–0.97) after adjusting for age, sex, hypertension, hyperlipidemia, and anti-diabetes agent use (including sulfonylureas, α -glucosidase, metformin, meglitinide, thiazolidinediones, and insulin).

DISCUSSION

In this population-based, retrospective study, we found that combined use of TCM and Western medicine to treat T2DM exhibited a 33% reduced risk of stroke than using Western medicine alone. To our knowledge, this is the first population-based pharmacoepidemiological study that focused on the clinical benefit of adjunctive TCM in patients with T2DM to prevent subsequent stroke. Among various TCM therapies, our study showed that the most frequent TCM therapy in T2DM

TABLE 2. Top 10 Common Single Herbs Prescribed for Type 2 Diabetes in Users With Traditional Chinese Medicine

Single Herbs	TCM Users					
	Without Insulin Treatment (N = 873)			With insulin treatment (N = 175)		
	n (%)	Daily Dose (g)	Average Duration (Day)	n (%)	Daily dose (g)	Average duration (day)
	(TCM visits = 9365)			(TCM visits = 61687)		
<i>Dan-Shen (Salvia Miltiorrhiza)*</i>	3016 (4.89)	2.53	11.9	311 (3.32)	3.62	13.0
<i>Tian-Hua-Fen (Radix Trichosanthis)*, </i>	2462 (3.99)	2.96	11.1	407 (4.35)	1.61	10.7
<i>Huang-Qi (Radix Astragali)‡,¶</i>	2215 (3.59)	1.60	11.9	303 (3.24)	1.38	9.54
<i>Shan-Yao (Rhizoma Dioscoreae)‡,¶</i>	1927 (3.12)	1.49	11.7	303 (3.24)	1.23	9.84
<i>Ge-Gen (Radix Puerariae)†,‡</i>	1632 (2.65)	1.23	11.2	218 (2.33)	1.29	11.2
<i>Shi-Hu (Herba Dendrobii)#</i>	1456 (2.36)	2.58	11.0	211 (2.25)	1.51	9.72
<i>Xuan-Shen (Radix Scrophulariae)‡,¶</i>	1438 (2.33)	1.77	11.6	184 (1.96)	1.06	10.3
<i>Mai-Men-Dong (Radix Ophiopogonis)†,§, </i>	1234 (2.00)	2.27	10.7	143 (1.53)	1.08	11.2
<i>Cang-Zhu (Rhizoma Atractylodis)*,**</i>	1044 (1.69)	1.23	11.5	125 (1.33)	1.13	11.6
<i>Da-Huang (Radix et Rhizoma Rhei)*,¶</i>	964 (1.56)	1.20	10.8	429 (4.58)	0.59	10.1

T2DM = type 2 diabetes mellitus; TCM = traditional Chinese medicine.

* Anti-inflammation.

† Increase in insulin secretion.

‡ Enhancement of glucose uptake by adipose and muscle tissues.

§ Inhibition of glucose absorption by the intestine.

|| Inhibition of glucose production by hepatocytes.

¶ Decrease in insulin resistance or enhancement of insulin sensitivity.

Prevention of diabetic cataract.

** Neuroprotective effect.

patients were CHPs (78.2%), followed by acupuncture (12.6%) and manipulative therapy (6.61%).

Chronic subclinical inflammation is associated with insulin resistance, a situation of increased risk for developing diabetes and cardiovascular events.^{10,11} Clinical evidence showed that the

risk and outcome of stroke is highly associated with inflammatory burden.¹² In our study, the top 4 herbs most commonly prescribed in the treatment of T2DM patients have been reported to exert a hypoglycemic effect via their anti-inflammatory mechanism, including *Dan-Shen (Salvia Miltiorrhiza)*,¹³ *Da-Huang (Radix*

TABLE 3. Top 10 Common Herbal Formulae Prescribed for Type 2 Diabetes in Users With Traditional Chinese Medicine

Herbal Formulae	TCM Users						Reference
	Without Insulin Treatment (N = 873)			With Insulin Treatment (N = 175)			
	n (%)	Daily Dose (g)	Average Duration (Day)	n (%)	Daily dose (g)	Average duration (day)	
	(TCM visits = 6158)			(TCM visits = 35,560)			
<i>Liu-Wei-Di-Huang-Wan</i>	2813 (7.91)	9.06	11.0	430 (6.98)	9.55	10.7	24,25
<i>LWDHW derivatives</i>							
<i>Zhi-Bo-Di-Huang-Wan</i>	1727 (4.85)	7.77	13.1	403 (6.54)	5.66	11.3	None
<i>Ji-Sheng-Shen-Qi-Wan</i>	1117 (3.14)	14.6	12.0	176 (2.86)	11.5	10.6	None
<i>Qi-Ju-Di-Huang-Wan</i>	1117 (3.14)	6.42	13.2	153 (2.46)	4.15	12.6	None
<i>Ba-Wei-Di-Huang-Wan</i>	781 (2.20)	12.6	12.5	189 (3.07)	11.7	12.6	26–33
<i>Bai-Hu-Jia-Ren-Shen-Tang</i>	2158 (6.07)	7.70	11.8	288 (4.68)	3.90	10.7	37–39
<i>Yu-Quan-Wan</i>	2009 (5.65)	5.64	11.5	606 (9.84)	4.81	12.1	None
<i>Bai-Hu-Tang</i>	1046 (2.94)	17.3	11.4	142 (2.31)	4.27	10.0	34–36
<i>Gan-Lu-Yin</i>	992 (2.79)	7.27	11.4	113 (1.84)	3.96	9.86	None
<i>Xue-Fu-Zhu-Yu-Tang</i>	702 (1.97)	7.54	13.1	115 (1.87)	2.41	10.1	None

LWDHW = *Liu-Wei-Di-Huang-Wan*; T2DM = type 2 diabetes mellitus; TCM = traditional Chinese medicine.

TABLE 4. Incidence and Hazard Ratio of Stroke, Diabetic Foot and CKD Among TCM and Non-TCM Users

	Non-TCM Users (N = 4092)		TCM Users (N = 1,049)		IRR (95% CI) [†]	HR (95% CI) [‡]
	Event No.	IR [§]	Event No.	IR [§]		
Stroke	186	10.66	33	7.19	0.67 (0.47–0.98)*	0.67 (0.46–0.97)*
Diabetic foot	214	12.34	53	11.63	0.94 (0.70–1.27)	0.93 (0.69–1.26)
CKD	525	31.77	156	36.73	1.16 (0.97–1.38)	1.11 (0.93–1.33)

Non-TCM users are 1:4 frequency matched with TCM users.

CI = confidence interval; CKD = chronic kidney diseases; HR = hazard ratio; IR = incidence rate; IRR = incidence rate ratio; TCM = traditional Chinese medicine.

[†] Using Poisson regression.

[‡] Adjusted for age, sex, hypertension, hyperlipidemia, and anti-diabetes agent use (including sulfonylureas, α -glucosidase, metformin, meglitinide, thiazolidinediones and insulin) using Cox proportional hazard regression.

[§] Per 1000 person-years.

* $P < 0.05$.

et Rhizoma Rhei),¹⁴ *Tian-Hua-Fen (Radix Trichosanthis)*,¹⁵ and *Huang-Qi (Radix Astragalii)*.¹⁶ Other than Chinese herbal medicine, acupuncture could also take part in the anti-inflammatory mechanism by enhancing vagus nerve activity.¹⁷ Since inflammation participates in the pathogenesis of T2DM and subsequent stroke,¹⁸ TCM with anti-inflammation mechanisms could exert not only hypoglycemic effects but also potential effects to prevent subsequent stroke through anti-inflammatory mechanisms. Previous study also elucidated that the type 2 ryanodine receptor, a calcium release channel, exists in cardiomyocytes and pancreatic β cells and plays a crucial role in oxidative stress, which mechanically explains the relationship between cardiovascular disease and diabetes.¹⁹ Further studies focus on the mechanism how TCM work on the calcium channel is a potential research direction.

In the clinical practice, insulin injection means an increased severity of T2DM. For TCM practitioners, insulin use also means a progressed stage that needs more intensive treatment. We divided TCM users into 2 groups, 1 with insulin and 1 without, to observe the different prescription pattern between the 2 groups. In our study, the most common single herb for T2DM was *Dan-Shen (Radix Salviae Miltiorrhizae)* in patients without insulin use, compared with *Da-Huang (Radix et Rhizoma Rhei)* in patients who received insulin treatment. *Dan-Shen*, the roots and rhizomes of *Radix Salviae Miltiorrhizae*, is an important Chinese medicine widely used to promote blood circulation, remove blood stasis, and treat coronary heart diseases. It is often used in herbal formulae to treat diabetic complications. The combination of *Radix Salviae Miltiorrhizae* and *Cortex Moutan* prevents diabetes-induced vascular damage and produces significant cerebrovascular protective effects through the reduction of oxidative stress and through intracellular calcium regulatory mechanisms.²⁰ *Dan-shensu*, the main active component of *Dan-Shen*, protects endothelial cells from the damage induced by H_2O_2 and inhibits apoptosis.²¹ On the other hand, *Da-Huang*, the roots and rhizomes of *Rheum palmatum L.*, *Rheum tanguticum Maxim. ex Balf.*, or *Rheum officinale Baill.*, is used as laxative to clear heat, remove toxicity, activate blood, and dispel stasis according to TCM theory. Emodin, the major bioactive component of *Da-Huang*, significantly decreases the levels of blood glucose, triglyceride, and total cholesterol in STZ-induced diabetic mice through the activation of PPAR- γ and the modulation of

metabolism-related genes.²² The glucose tolerance and insulin sensitivity in the emodin-treated group were significantly improved compared with the controls. Furthermore, emodin is considered a potent and selective inhibitor of 11 β -hydroxysteroid dehydrogenase type 1 which is an attractive therapeutic target of T2DM.²³ As a result, using insulin treatment as a cut point of different stages in T2DM, TCM practitioners use *Dan-Shen* to protect vascular endothelium in the early stage without insulin treatment and use *Da-Huang* to enhance hypoglycemic effect in the late stage with insulin use. We found difference in single herb prescription pattern between insulin and noninsulin patients, indicating corresponding TCM strategies for various conditions in T2DM.

In addition, there is also a different herbal formula prescription pattern between insulin and noninsulin population. The most common herbal formula for T2DM was *Liu-Wei-Di-Huang-Wan* in patients without insulin use, compared with *Yu-Quan-Wan* in patients who received insulin treatment. According to the concepts of TCM, T2DM is a systemic disease with yin-deficiency, which causes heat accumulation and blood stasis in the body and eventually leads to subsequent complications. In TCM theory, *Liu-Wei-Di-Huang-Wan* is used to nourish yin and tonify the liver and kidney. *Yu-Quan Wan* is used to treat polydipsia by clearing heat, generating body fluids, quenching thirst, and moistening dryness, which are obvious symptoms in hyperglycemic state. Among the top 10 common herbal formulae, 4 CHPs, *Zhi-Bo-Di-Huang-Wan*, *Ji-Sheng-Shen-Qi-Wan*, *Qi-Ju-Di-Huang-Wan*, and *Ba-Wei-Di-Huang-Wan*, are derivative formulae of *Liu-Wei-Di-Huang-Wan*. Similar to another study in Taiwan,³ *Liu-Wei-Di-Huang-Wan* and its derivatives were found to be the most common herbal formulae prescribed by TCM doctors for the treatment of diabetes in Taiwan. Recent scientific evidence has suggested that *Liu-Wei-Di-Huang-Wan* reduced blood glucose, relieved neuropathy and nephropathy in diabetes,²⁴ and improved the lipid profile to reduce cardiovascular risk.²⁵ Animal studies revealed that *Ba-Wei-Di-Huang-Wan* increased insulin synthesis and release,^{26,27} suppressed the release of glucose from the liver,²⁶ normalized or suppressed the small intestinal disaccharidase activity,²⁸ reduced the damage caused by oxidative stress,^{29,30} and prevented diabetic nephropathy.^{31–33}

Another formula, *Bai-Hu-Tang*, and its derivative, *Bai-Hu-Jia-Ren-Shen-Tang*, were also frequently used in T2DM.

Bai-Hu-Tang, traditionally used to reduce fever heat and promote generation of body fluids, played an important role in immunity protection and anti-inflammation.^{34,35} Moreover, *Bai-Hu-Tang* stimulated glucose uptake in adipocytes via PPAR- γ activation rather than the insulin signaling pathway.³⁶ *Bai-Hu-Jia-Ren-Shen-Tang* (same as Byakko-ka-ninjin-to in Kampo medicine) has hypoglycemic effect and acts as a facilitatory agent on salivary secretion to reduce xerostomia in T2DM patients.^{37–39} Evidence of *Gan-Lu-Yin* focused on antitumor effect, including inhibiting angiogenesis⁴⁰ and suppressing vascular smooth muscle cell migration.⁴¹ *Xue-Fu-Zhu-Yu-Tang*, traditionally used to promote the circulation of blood to remove blood stasis and activate the flow of Qi to relieve pain, demonstrated potency to antiplatelet aggregation,⁴² decrease in the serum total triglyceride concentration, and suppression of proinflammatory cytokines in high cholesterol-fed rats.⁴³ Lack of scientific research on *Yu-Quan-Wan*, *Gan-Lu-Yin*, and *Xue-Fu-Zhu-Yu-Tang* in treating T2DM, further investigation on these 3 herbal formulae in T2DM is necessary.

Other than CHPs, we found that acupuncture is also a widely used treatment in T2DM. Previous randomized controlled trials showed that electroacupuncture (EA) and rosiglitazone combined therapy improved insulin resistance through a reduction in plasma free fatty acid.⁴⁴ EA enhanced insulin sensitivity and improved glucose tolerance through activating cholinergic nerves and nitric oxide synthase, which lower plasma free fatty acid levels.^{45–47} Moreover, acupuncture stimulation showed potential neuroprotective effects through suppression of cerebral blood flow response in the increased plasma osmolality and extracellular changes in glutamate in diabetic rats under ischemic conditions.⁴⁸ In the above studies, the most common acupoints used in T2DM were located at the abdomen and legs, including Zhongwan (CV-12), Gwanyuan (CV-4), Zusanli (ST-36), Yanglingquan (GB-34), and Xuanzhong (GB-39).

One of this study's strengths is that we obtained the data from the NHI database, which is a government-run, single-payer NHI program that covers more than 97% of Taiwanese citizens and over 99% of Taiwanese healthcare institutes.⁷ This ensures that the present study is representative of the general population with minimal selection bias, thereby offering a comprehensive account of the subsequent stroke of both TCM and non-TCM users. The large sample size gave adequate power for stratification into subgroups for statistical analysis. There are several limitations. First, we did not choose 2 other common complications, neuropathy and retinopathy, as the endpoint. It was difficult to define DM-related neuropathy and retinopathy since they are progressive and the diagnosis codes could be varied among different physicians in different clinical conditions. Second, although we did not have the exact value of blood glucose or glycated hemoglobin (HbA1c) of every patient because of the limitation of the NHI database, we could evaluate the long-term treatment effect by the incidence of subsequent vascular events. Third, people using TCM may tend to focus on maintaining good health and have healthier lifestyle modification. Because of the nature of NHIRD, some variables that contribute to the propensity to stroke, such as exposure to cigarette smoke, obesity, and alcohol consumption, were not collected in this database. A future study including information on lifestyle will be helpful. We are currently designing a long-term follow-up study of diabetes patients in our hospital to evaluate the protective effects of adjunctive TCM therapy in diabetes patients. Meanwhile, this population-based large-scale retrospective analysis of the NHIRD still provides some valuable information on the

association of TCM therapy and vascular complications among patients with T2DM.

In conclusion, this population-based, retrospective cohort study shows that the concurrent TCM use may decrease the risk of stroke in T2DM patients. Our study results suggest that the use of TCM as an adjunctive therapy in patients with T2DM may prevent subsequent stroke. Further long-term prospective studies are required to validate these findings.

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