

Hormone therapy in postmenopausal women associated with risk of stroke and venous thromboembolism: a population-based cohort study in Taiwan

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Abstract

Objective: The aim of the study was to evaluate the risks and benefits of hormone therapy (HT) in postmenopausal women in Taiwan.

Methods: A retrospective cohort study was conducted using the Taiwan National Health Insurance Research Database, a population-based healthcare claims dataset. Eligible women, aged 40 to 65, were matched 1:1 by age and menopause year to avoid confounding through imbalanced baseline characteristics among the two groups (2,491 pairs). The primary outcomes were acute coronary syndrome (ACS), venous thromboembolism (VTE), and ischemic stroke (IS).

Results: Mean follow-up in the HT group was 30 months. Mean age of the HT group was 50 years. After adjusting for age, statin and anticoagulant use, hyperlipidemia, diabetes, and hypertension, the hazard ratios (95% CIs) for the HT group were increased: ACS, 3.73 (2.01-6.91); IS, 3.51 (2.41-5.11); and VTE, 2.51 (1.15-5.47).

Conclusions: In postmenopausal Taiwanese women, HT may be associated with an increased risk of cardiovascular disease. Although the women in our population receiving HT were near menopausal age, their risk of cardiovascular disease was still higher than in the non-HT group.

Key Words: Coronary syndrome – Hormone therapy – Menopause – Stroke – Thromboembolism.

Hormone therapy (HT), which is usually a combination of estrogen and progestin, has been used to improve quality of life among women with menopausal symptoms and prevent osteoporosis in postmenopausal women.¹ Nevertheless, the Women's Health Initiative (WHI) study revealed that HT in postmenopausal women caused an increase in various comorbidities, including coronary heart disease (CHD), stroke, breast cancer, and pulmonary embolism, but a decrease in endometrial cancer, colorectal cancer, and hip fracture.^{2,3} Possible mechanisms of increased thrombotic risk after HT may result from a preexisting endothelial injury, the formation of fibrin fibers, hemostasis imbalance, or an estrogen receptor-mediated dysfunction.^{4,5}

HT can be prescribed as local (cream, pessary, and ring) or systemic therapy (oral medication, transdermal patches, and implants).⁶ Hormone ingredients can be prepared as estrogen alone, estrogen combined with progestin, selective estrogen receptor modulators (SERMs), and gonadomimetics (tibolone).⁷ The various schedules of HT include consumption of estrogen daily, sequential consumption of estrogen combined with progestin for 14 days, and continuous consumption of estrogen combined with progestin daily. Commonly used estrogen derivatives include conjugated equine estrogen (CEE), 17-beta-estradiol, and ethinyl estradiol. Moreover, commonly used progestin derivatives include medroxyprogesterone acetate (MPA) and norethindrone acetate. The most common dose of HT for a patient with an intact uterus is 0.625 mg CEE combined with 2.5 mg MPA.⁸ An estrogen-only prescription is provided to a patient without a uterus. SERMs can be HT alternatives for preventing and treating osteoporosis.⁹ The International Menopause Society suggests that HT can be initiated before the age of 60 years or within 10 years of menopause.¹⁰

Prescription amounts, however, have decreased rapidly over the last decade since the WHI study was published.² More varied modalities for HT were required, and individualized care for postmenopausal women with short-term HT use, small dosages, and personalized medicine was recommended. The use of progestin was decreased or replaced by SERMs.¹¹ Progestin intrauterine devices were also used off-label to protect the uterus while receiving HT with estrogen.¹¹

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Recently, the WHI study, a long-term follow-up study, showed that HT was not associated with the risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up period of 18 years.¹²

The risk–benefit ratio for women receiving HT may differ by race and ethnicity. US population data demonstrated that risks of underlying cancer and heart disease were significantly lower in Asian-American than in white women.^{13,14} The participants in the studies cited were, however, mostly white, and therefore the risks and benefits of HT for Asian women may differ from those for white women.

The aim of this study was to determine the risk of acute coronary syndrome (ACS), ischemic stroke (IS), and venous thromboembolism (VTE) in postmenopausal women receiving HT in Taiwan based on a high-quality national health database.

METHODS

Data source

The data source was the Longitudinal Health Insurance Database (LHID) for the period from 2000 to 2011.¹⁵ The Health and Welfare Statistics Application Center of the Taiwan Ministry of Health and Welfare provided the database. The LHID, comprising medical claim data from 2 million beneficiaries, was randomly sampled from year 2000 registry of all National Health Insurance (NHI) enrollees. The data included demographic characteristics, inpatient and outpatient visits, medications, and disease diagnoses based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). This study was approved by the Research Ethics Committee of Hualien Tzu Chi Hospital (IRB no. 103-163-C).

Study design and follow-up

A retrospective population-based cohort study was conducted to investigate the risk of vascular disease among postmenopausal women receiving HT. In our study, postmenopausal women were defined according to one of the following criteria: (1) receiving diagnoses of menopause (ICD-9-CM code 627) at least 2 times during 2001 to 2010; (2) receiving a diagnosis of menopause from a gynecological outpatient clinic at least once; and (3) being aged between 40 and 65 years at first menopausal syndrome diagnosis. We excluded women who (1) had their first diagnosis of menopause before 2001 or after 2010; (2) had a prior diagnosis of vascular disease (ICD-9-CM codes 410-414, 430, 431, 433, 434, 436, 415.1, 451, 453) before the index date; (3) underwent bilateral oophorectomy concomitantly (ICD-9-CM codes 65.5, 65.6; Diagnosis Related Groups [DRG] codes 0359D, 0359F); or (4) had any type of malignancy (ICD-9-CM codes 140-208). A total of 44,554 women were selected for the study cohort.

To compare the effect of HT on vascular disease risk in postmenopausal women, we divided the women into two groups. The HT group ($n = 7,312$) included postmenopausal

women who were treated with HT for at least 28 days and received no alternative therapies during follow-up. The non-HT group ($n = 3,507$) included postmenopausal women who did not receive HT or any alternative therapies during follow-up. In our study, HT for relieving menopausal symptoms was defined as therapy using orally administered estrogen, progesterone, allylestrenol, norethindrone, or medroxyprogesterone. The cumulative days of drug use were measured as the total days of drug use between the first menopause diagnosis date and the endpoint. The index date for the HT group was defined as the prescription date when the total number of days of HT drug use was more than 28. Women receiving HT for less than 28 days or alternative therapies such as Chinese herbal medicine were excluded ($n = 33,735$). Finally, a total of 10,819 eligible women were enrolled (HT = 7,312, non-HT = 3,507).

Matching criteria and covariate measurement

We performed 1:1 matching of participants by age and menopause year to avoid confounding through imbalanced baseline characteristics between the two groups (2,491 pairs) (Fig. 1). Baseline comorbidities and medication history at 6 months before the index date were ascertained. Comorbidities considered in this study included hyperlipidemia (ICD-9-CM code 272), diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401-405), peripheral arterial occlusive disease (ICD-9-CM code 443.9), and heart failure (ICD-9-CM code 428). Medication history included antiplatelet, anticoagulant, statin, and hemostatic therapy. ICD-9-CM codes were used to identify the outcome variables for vascular disease during follow-up (ACS: ICD-9-CM codes 410, 411; IS: ICD-9-CM codes 433, 434, 436; VTE: ICD-9-CM codes 415.1, 451, 453). We used the earliest incident of the following events as the endpoint: (1) occurrence of any vascular disease, (2) 1 year after the last HT prescription date, (3) death, and (4) December 31, 2011. For three different events, we followed up each occurrence separately. Thus, the three events could not affect the incidence of one another. We included only women who were experiencing a first event occurrence.

Statistical analysis

To compare the HT and non-HT groups, we used an independent sample *t* test for continuous variables and a chi-squared test for categorical variables. Cox proportional hazard models were used to estimate the 95% CIs and the hazard ratios (HRs) of vascular diseases associated with HT use. The model was adjusted for potential confounding factors such as age, hypertension, diabetes mellitus, hyperlipidemia, hemostatics, and statin therapy. The trend of HT use was also calculated. Furthermore, we excluded women with a menopause diagnosis before 2003 from the sensitivity analysis. Data analysis was performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC) and Stata version 13 (LP. 2013; StataCorp, College Station, TX). Two-sided $P < 0.05$ was considered statistically significant.

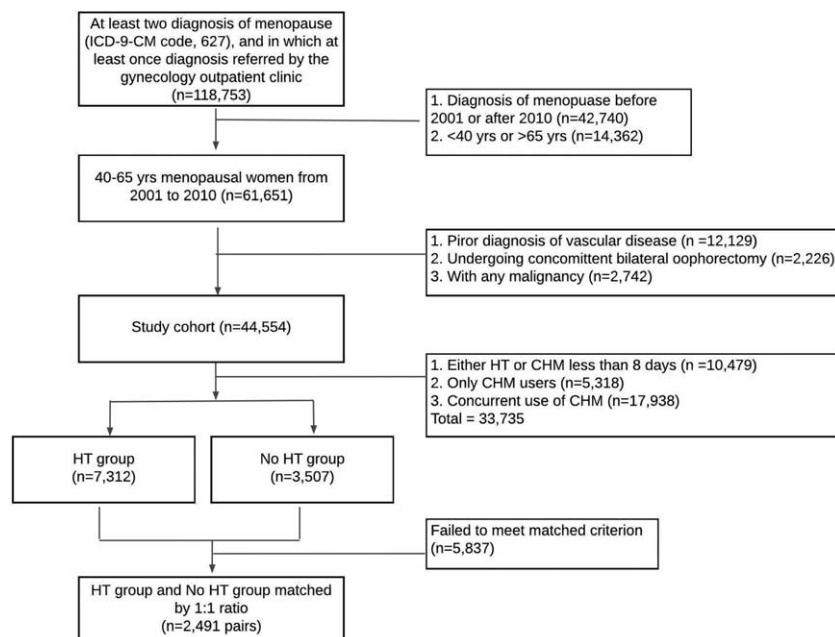


FIG. 1. Study flow chart. CHM, Chinese herbal medicine; HT, hormone therapy.

RESULTS

A total of 10,819 women were eligible for this study (HT = 7,312, non-HT = 3,507). The average duration of HT use was 235 days. After matching, women in the two groups were comparable in age and menopause year (Table 1). The mean age of the participants was 50 years. Incidence rates of vascular diseases in the HT group were significantly higher than in the non-HT group (ACS: 4.4 vs 1.6 per 1,000 person-y, $P < 0.01$; IS: 13.4 vs 4.3 per 1,000 person-y, $P < 0.01$; VTE: 2.4 vs 1.1 per 1,000 person-y, $P < 0.01$).

Table 2 shows that women in the HT group had significantly higher risks of ACS (HR = 3.73; 95% CI, 2.01-6.91), IS (HR = 3.51; 95% CI, 2.41-5.11), and VTE (HR = 2.51; 95% CI, 1.15-5.48) compared with those in the non-HT group.

In the sensitivity analysis, we again found that women in the HT group had higher risks of IS (HR = 2.43; 95% CI, 1.43-4.11) and VTE (HR = 2.51; 95% CI, 1.15-5.48) (Table 3). The number of the women receiving HT dropped dramatically after 2002 (Fig. 2), reflecting the findings of the WHI study in that year.

We used a time-dependent Cox proportional model to compare the risk of event occurrence, and we performed sensitivity analysis using different time-window lengths (Supplemental Table 1, <http://links.lww.com/MENO/A346>). All analysis results obtained using the different time-window lengths were consistent. Hence, HT use was associated with a higher risk of IS and VTE.

DISCUSSION

In this study, the mean age of women who received HT (the HT group) was 50 years (Table 1), which is younger than that for women who receive HT in western countries.² We found that vascular events (ACS, IS, and VTE) had a higher frequency

in the HT than the non-HT group (Table 1), which was consistent with the findings of other studies.^{2,16} We also found that the HT group had a higher risk of IS and VTE (Supplementary Table 1, <http://links.lww.com/MENO/A346>).

The validation of ICD-9-CM codes for IS,¹⁷ ACS,¹⁸ and VTE in the National Health Insurance Research Database (NHIRD) has been reported before. The positive predictive value (PPV) of a diagnosis of IS in the NHI claims data was high (94.51%).¹⁹ Of the 338 ACS cases, 297 were confirmed by clinical and laboratory data, yielding a PPV of 88%.¹⁸ Compared with another database with a PPV of 60.8%,²⁰ using ICD-9-CM codes to search for IS, ACS, and VTE in the NHIRD achieved high PPVs.

A prospective double-blind randomized control trial (RCT) showed increased VTE risk after receiving HT,²¹ and a population-based study similarly showed that HT was associated with a higher risk of VTE, albeit this was limited to the first year of use.²² A meta-analysis suggested that oral estrogen increased the risk of VTE, especially during the first year of treatment.²³ Researchers are nearly unanimous that HT can increase the risk of VTE.²⁴ In our study, the risk of VTE for the HT group was higher than that for the control group.

One meta-analysis of clinical trials of HT reported an approximately 30% increased risk of IS.²⁵ Another prospective cohort study including 16,906 women (45-73 y old, 10.5-y follow-up) showed no significant association between HT and the risk of total stroke.²⁶ One study, however, found that although early initiation of HT (0-5 y after menopause) was not associated with stroke risk, late initiation increased the risk of stroke.²⁷ Another report showed that discontinuation of HT was associated with a high risk of stroke death in the first year of postmenopausal HT.²⁸ We suggest that the association of HT with stroke may depend on the age of women receiving

TABLE 1. Characteristics of HT and no use groups

	Before match		P	After match		P
	HT (n = 7,312)	No use (n = 3,507)		HT (n = 2,491)	No use (n = 2,491)	
Age	49.78 ± 5.25	51.31 ± 5.27	<0.01 ^a	50.61 ± 5.17	50.61 ± 5.17	1.00
Year of menopause			<0.01 ^a			1.00
2001	1,870 (25.57%)	348 (9.92%)		321 (12.89%)	321 (12.89%)	
2002	1,067 (14.59%)	266 (7.58%)		232 (9.31%)	232 (9.31%)	
2003	518 (7.08%)	221 (6.30%)		168 (6.74%)	168 (6.74%)	
2004	609 (8.33%)	275 (7.84%)		216 (8.67%)	216 (8.67%)	
2005	524 (7.17%)	291 (8.30%)		212 (8.51%)	212 (8.51%)	
2006	533 (7.29%)	303 (8.64%)		212 (8.51%)	212 (8.51%)	
2007	502 (6.87%)	393 (11.21%)		251 (10.08%)	251 (10.08%)	
2008	596 (8.15%)	400 (11.41%)		266 (10.68%)	266 (10.68%)	
2009	537 (7.34%)	470 (13.40%)		294 (11.80%)	294 (11.80%)	
2010	556 (7.60%)	540 (15.40%)		319 (12.81%)	319 (12.81%)	
Comorbidity						
Hypertension	818 (11.19%)	387 (11.04%)	0.81	125 (5.02%)	110 (4.42%)	0.31
Diabetes mellitus	340 (4.65%)	168 (4.79%)	0.74	315 (12.65%)	255 (10.24%)	0.01 ^a
Hyperlipidemia	328 (4.49%)	204 (5.82%)	<0.01 ^a	135 (5.42%)	130 (5.22%)	0.75
Atrial fibrillation	84 (1.15%)	36 (1.03%)	0.57	39 (1.57%)	23 (0.92%)	0.04 ^a
Heart failure	18 (0.25%)	5 (0.14%)	0.27	7 (0.28%)	4 (0.16%)	0.36
Atherosclerosis	34 (0.46%)	5 (0.14%)	<0.01 ^a	13 (0.52%)	4 (0.16%)	0.02 ^a
PAOD	10 (0.14%)	10 (0.29%)	0.09	3 (0.12%)	7 (0.28%)	0.20
Drug use before index date						
Anticoagulants	21 (0.29%)	10 (0.29%)	0.98	8 (0.32%)	8 (0.32%)	1.00
Antiplatelets	169 (2.31%)	65 (1.85%)	0.12	48 (1.93%)	38 (1.53%)	0.27
Hemostatics	761 (10.41%)	316 (9.01%)	0.02 ^a	267 (10.72%)	219 (8.79%)	0.02 ^a
Statins	228 (3.12%)	146 (4.16%)	<0.01 ^a	105 (4.22%)	91 (3.65%)	0.30
Outcome						
ACS						
Follow-up, mo	34.47 ± 28.05	—	—	30.75 ± 25.27	65.38 ± 37.91	<0.01 ^a
Event	101 (1.41%)	26 (0.74%)	<0.01 ^a	28 (1.13%)	22 (0.89%)	0.39
Incident rate (1,000 person-y)	4.8	—	—	4.4	1.6	<0.01 ^a
IS						
Follow-up, mo	34.00 ± 27.96	—	—	29.39 ± 23.85	64.58 ± 38.11	<0.01 ^a
Event	373 (5.10%)	71 (2.02%)	<0.01 ^a	82 (3.29%)	57 (2.29%)	0.03 ^a
Incident rate (1,000 person-y)	18.0	—	—	13.4	4.3	<0.01 ^a
VTE						
Follow-up, mo	34.60 ± 28.12	—	—	30.36 ± 24.68	65.67 ± 37.85	<0.01 ^a
Event	56 (0.78%)	16 (0.46%)	0.06	15 (0.60%)	15 (0.60%)	1.00
Incident rate (1,000 person-y)	2.7	—	—	2.4	1.1	<0.01 ^a

Data are shown by mean ± SD or proportion of the character.

ACS, acute coronary syndrome; HT, hormone therapy; IS, ischemic stroke; PAOD, peripheral arterial occlusive disease; VTE, venous thromboembolism.

^aP < 0.05.

HT. In our study, women with a mean menopausal age of 50 years receiving HT had an increased risk of stroke (Tables 2 and 3).

Contemporarily, clinical data on the association between HT and ACS are available from more than 40 observational

studies and 7 RCTs.^{2,29} Most of these studies included women who used unopposed estrogen. Limited data are available from observational studies on estrogen and progesterone therapy.³⁰ A meta-analysis of 40 observational studies suggested that a 50% reduction in CHD risk was associated with

TABLE 2. Hazard ratio (HR) for event of HT and no use groups based on match cohort

Event	Group	Event n (%)	Follow-up, mo	HR	95% CI
ACS	No use	22 (0.89)	65.38 ± 37.91	1	—
	HT	28 (1.13)	30.75 ± 25.27	3.73	(2.01-6.91) ^a
IS	No use	57 (2.29)	64.58 ± 38.11	1	—
	HT	82 (3.29)	29.39 ± 23.85	3.51	(2.41-5.11) ^a
VTE	No use	15 (0.60)	65.67 ± 37.85	1	—
	HT	15 (0.60)	30.36 ± 24.68	2.51	(1.15-5.47) ^a

Cox regression analyses were adjusted for age, hypertension, diabetes mellitus, hyperlipidemia, hemostatics, and statins therapy.

ACS, acute coronary syndrome; HT, hormone therapy; IS, ischemic stroke; VTE, venous thromboembolism.

^aP < 0.05.

TABLE 3. Sensitivity analysis of HRs for event of HT use and no use groups (women with a diagnosis of menopause before 2003 were removed)

Event	Group	Event n (%)	Follow-up, mo	HR	95% CI
ACS	No use	10 (0.52)	51.35 ± 28.35	1	—
	HT	10 (0.52)	27.04 ± 20.05	2.18	(0.85-5.58)
IS	No use	27 (1.39)	51.47 ± 28.41	1	—
	HT	36 (1.85)	26.97 ± 20.43	2.42	(1.43-4.10) ^a
VTE	No use	6 (0.32)	52.02 ± 28.22	1	—
	HT	8 (0.42)	27.58 ± 20.62	2.51	(1.15-5.47) ^a

Cox regression analyses were adjusted for age, hypertension, diabetes mellitus, hyperlipidemia, hemostatics, and statins therapy.

ACS, acute coronary syndrome; HT, hormone therapy; IS, ischemic stroke; VTE, venous thromboembolism.

^aP < 0.05.

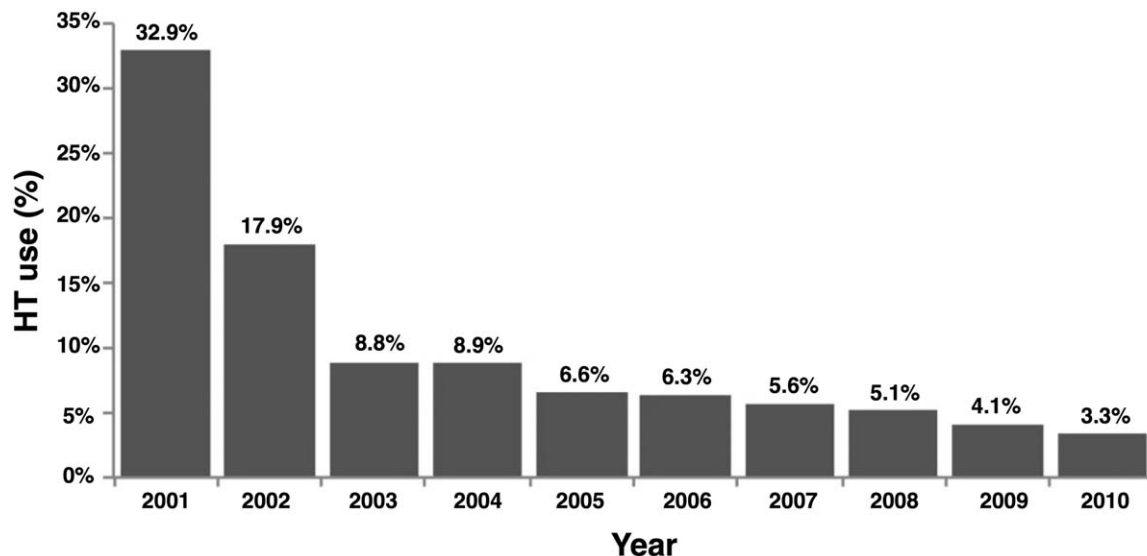


FIG. 2. Percentage of women receiving hormone therapy from 2001 to 2010. HT, hormone therapy.

current estrogen use.³¹ In our population-based study, women receiving HT, including estrogen, progesterone, allylestrenol, norethindrone, or medroxyprogesterone, had an increased risk of ACS (Tables 1-3). This result matched that of the WHI study.

The North American Menopause Society found that for women who initiate HT more than 10 or 20 years from menopause onset or at the age of 60 years or older; the risk–benefit ratio seemed less favorable because of the greater absolute risks of CHD, stroke, VTE, and dementia.³² Therefore, HT should be prescribed for short-term, low-dosage, and individualized treatment initiated early and near menopausal age. In our study, although the participants' mean age of 50 was near menopausal age, we nevertheless demonstrated associations between HT and high risks of ACS, IS, and VTE. Our study also revealed that the HT group exhibited a high risk of ACS, IS, and VTE at the 1-year follow-up point and also exhibited a high risk of IS and VTE at the 2- and 3-year follow-up points.

Progesterone and synthetic progestins showed varied effects on coagulation factors, lipids, insulin, and glucose. Therefore, they may differently affect cardiovascular risk, although data are insufficient.³³ Decreasing progestin usage was suggested after the WHI follow-up study.

Our original cohort included women who used alternative therapies. Because alternative therapies were not within the scope of our study, we excluded a relatively high number of women who used alternative therapies ($n = 33,735$), and only 10,819 women were included in this study. A previous study showed that women receiving HT combined with alternative therapy using Chinese herbal medicine had a lower occurrence of IS than did women receiving HT only (HR = 0.3, 95% CI = 0.21-0.43)³⁴; however, no comparison with a non-HT group was performed. In our study, the risk of cardiovascular disease (CVD) in the HT group was adjusted for comorbidities. HT alone can contribute to an increased risk of CVD.

Two studies in Taiwan (based on the NHIRD) have examined the association between HT and the risk of CVDs. One study showed that CEE with or without MPA was not associated with increased rates of CHD,³⁵ which contrasts with the high rate of ACS (CHD) in the present study. That study, however, showed that CEE with MPA was associated with a higher rate of breast cancer,³⁵ which we did not examine. Our study differed from that one in the age of the participants (40-59 y vs 50-79 y) and the study period (2000-2011 vs 1997-2007). Another study showed a declining trend of HT use after the 2002 WHI study,³⁶ and our study showed the same trend in HT use from 2002 to 2010.

The present study has several strengths. First, it was a cohort study using a nationwide population-based database containing the data of approximately 24 million individuals, which enabled precise evaluation of the association between HT and the risk of ACS, VTE, and stroke. Second, a cohort study is the most suitable method for exploring the association between HT and cardiovascular events. Finally, the Taiwan NHI program covers nearly the entire population of Taiwan, and all medical records can be accurately traced through the NHIRD. Thus, it was possible to follow up on HT patients with or without ACS, VTE, or stroke under the NHIRD program. Additionally, we matched the reference cohort using the primary confounding factor, namely age.

Nevertheless, this study also has limitations. First, it had a short follow-up time (the NHIRD covers only 12 years). Second, although the reference cohort was selected by matching for age, the primary confounding factor, and obtained a robust estimate of HRs through multivariate analyses, other such factors were not considered. Third, only the oral intake of estrogen was included in this study; other forms of intake, such as dermal or vaginal, and other hormones, such as progesterone, were not considered. Finally, our database could not be controlled for lifestyle and behavioral factors (eg, diet and exercise), which could be significant

confounders. Therefore, these results have only modest statistical precision, and should be interpreted with caution.

CONCLUSIONS

In postmenopausal Taiwanese women, HT may be associated with increased risk of CVD. Although the women receiving HT in our population were near menopausal age, their risk of CVD was still higher than that for women not receiving HT. Further investigation of this population is warranted.

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