Original Article
Yonsei Med J 2025 Jul;66(7):429-437
https://doi.org/10.3349/ymj.2024.0053
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Menopausal Hormone Therapy and the Risk of Stroke: A Nationwide Cohort Study

Sung Pil Choo[1]*, Hyunji Park[2]*, Hyemin Park[3], Inha Lee[3], Sihyun Cho[3], Changsoo Kim[4,5], Kyung-Yul Lee[6], Jae Hoon Lee[3], and Jong-Youn Kim[7]

[1]Department of Obstetrics & Gynecology, Inha University College of Medicine, Incheon;
[2]Department of Public Health, Yonsei University, Seoul;
[3]Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;
[4]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul;
[5]Institute of Human Complexity and Systems Science, Yonsei University, Incheon;
[6]Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;
[7]Department of Internal Medicine, Division of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

Purpose: Most studies have reported that the risk of coronary heart disease decreases when menopausal hormone therapy (MHT) is initiated before the age of 60 years or within 10 years of menopause. However, the findings regarding stroke risk remain conflicting. This study investigated the association between the risk of ischemic stroke and MHT, categorized by the type of MHT.

Materials and Methods: This population-based, retrospective cohort study was based on the Korean National Health Insurance Service-National Sample Cohort (2004–2015). Participants were aged 45–60 years with no cardiovascular disease or preexisting stroke, classified as never, past, and current users of MHT.

Results: Among the study participants, 16915 (88.77%) women had never undergone MHT, 1437 (7.54%) had previously undergone MHT, and 703 (3.69%) were currently using MHT. During the study period, with a mean follow-up of 11.23±2.13 years, the risk of ischemic events was significantly higher among current users [hazard ratio (HR): 2.98, 95% confidence interval (CI): 1.95–4.57, $p<0.001$], particularly in those using estrogen-only MHT (HR: 3.49, 95% CI: 1.12–10.90, $p=0.032$) and tibolone (HR: 3.52, 95% CI: 2.05–6.03, $p<0.001$), compared to never users. Meanwhile, no significant difference in the risk of ischemic events was observed between past users and never users, even after analyses accounting for estrogen type and progestin co-administration.

Conclusion: Women currently receiving MHT without underlying cardiovascular disease exhibited an increased risk of ischemic stroke, particularly those treated with E-only MHT or tibolone. However, this increased risk returned to baseline after discontinuing MHT, indicating that past use of MHT was not associated with an increased risk of ischemic stroke.

Key Words: Estrogen replacement therapy, ischemic stroke, ischemic attack, transient

Received: April 8, 2024 **Revised:** December 18, 2024 **Accepted:** December 26 2024 **Published online:** February 20, 2025
Co-corresponding authors: Jong-Youn Kim, MD, PhD, Department of Internal Medicine, Division of Cardiology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
E-mail: JYKIM0706@yuhs.ac and
Jae Hoon Lee, MD, PhD, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
E-mail: jhlee126@yuhs.ac

*Sung Pil Choo and Hyunji Park contributed equally to this work.
•The authors have no potential conflicts of interest to disclose.

INTRODUCTION

Menopausal hormone therapy (MHT) is used to treat vasomotor symptoms and genitourinary syndromes in peri- and postmenopausal women.[1] In the 1990s, based on observational studies, long-term utilization of MHT was widely prescribed as a preventative strategy against diseases in older adults, including coronary heart disease (CHD), stroke, dementia, and osteoporosis.[2-4] However, several clinical trials, including the Women's Health Initiative (WHI), indicated that MHT did not protect against cardiovascular disease; on the contrary, they raised concerns regarding an increased risk of cardiovascular disease, especially stroke.[5,6]

Ultimately, extension studies and subgroup analyses of clinical trials have revealed that the CHD risk increases only in women who begin MHT after the age of 60 or more than 10 years after reaching menopause.[7,8] Younger women have a reduced risk of developing CHD with MHT.[7] This so-called "window hypothesis" implies that the effects of MHT depend on the timing of MHT initiation and that positive health effects are greater with early initiation.

Unlike the consistent findings regarding CHD risk, conflicting results have been reported for ischemic stroke. A pooled analysis of five Swedish population-based cohort studies found no association between hormone therapy and stroke when initiated within 5 years after menopause.[9,10] Similarly, a prospective cohort study from Denmark reported an increased risk of ischemic stroke only in women with hypertension who were using hormonal therapy.[11] In contrast, a subgroup analysis of the WHI cohort found that women within 10 years of menopause assigned to the estrogen plus progestin (E+P) and estrogen-only (E-only) arms exhibited an elevated risk of ischemic stroke, regardless of the type of MHT administered.[12]

In addition to the timing of MHT initiation, factors such as the formulation, dosage, route of delivery, and lag time effect of MHT can also influence the estimation of stroke risk. For example, an increased risk of stroke with an increasing dose of estrogen was reported in the Nurses' Health Study.[13] Additionally, the co-administration of progestin with estrogen may impact the risk of stroke. Nevertheless, studies on the association between the various types of MHT and stroke risk are scarce in Korean women.

There are several reasons that may contribute to the differences in stroke risk associated with MHT among Korean women compared to existing studies. Most large-scale studies conducted in the United States and Europe during the 2000s primarily utilized conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA), which are not commonly used in South Korea. Furthermore, the 2013 International Menopause Society guidelines clarified the importance of initiating MHT before the age of 60 or within 10 years of menopause onset.[14] In this context, the present study aims to examine the relationship between stroke risk—specifically ischemic events and transient ischemic attacks (TIA)—and MHT among Korean women aged under 60 years, taking into consideration the type of MHT utilized.

MATERIALS AND METHODS

Data source and ethical considerations

The study population was recruited from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) database. The South Korean government operates a mandatory nationwide insurance system that covers all forms of health services, including hospitalization, ambulatory care, and pharmaceutical services. Details of the NHIS-NSC database are described elsewhere.[15] Briefly, the NHIS-NSC database is a public database created by the NHIS, encompassing a 2.2% sample (approximately 1 million individuals) of the South Korean population. This sample was systematically and randomly stratified, selected using proportional allocation across 1476 strata constructed based on participants' age, group, sex, eligibility status, and income level to represent the entire population of South Korea. Specifically, strata were defined by 18 age groups (infants under 1 year, ages 1–4, 5-year age groups between 5 and 79, and 80 years and above), two sex groups (male, female), and 41 income level groups (upper 20 percentiles for insured employees, lower 20 percentiles for insured self-employed individuals, and the lowest level of income for medical aid beneficiaries). The disease information of the participants was classified according to the 10th revision of the International Classification of Disease codes by primary care physicians, as well as in secondary and tertiary hospitals. The representativeness of the sample was examined by comparing it with the entire Korean population.[16,17] All identifiable personal data in the medical records were de-identified to comply with the Health Insurance Portability and Accountability Act privacy rule. The study protocol was approved by the Institutional Review Board of the hospital (Gangnam Severance Hospital IRB, approval number: 3-2020-0421). The Institutional Review Board waived the requirement for informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study population

A total of 551786 women enrolled in the NHIS-NSC, who underwent medical examinations from January 1, 2004, to December 31, 2015, were included in this study. Women younger than 45 years or older than 60 years at baseline and those who started MHT after the age of 60 years were excluded (n=470820). Women who had been prescribed MHT for less than 6 months during the study period were further excluded from the analyses. Women with the following diagnoses of risk factors for stroke during the washout period were also excluded from the study: preexisting TIA (n=430), preexisting ischemic stroke

https://doi.org/10.3349/ymj.2024.0053

(n=383), acute myocardial infarction (n=470), coronary artery disease (n=47), peripheral vascular disease (n=4530), malignancy (n=3571), atrial fibrillation (AF) (n=506), and use of antithrombotic drugs (n=1145) (Supplementary Fig. 1, only online). The washout period was defined as a period at least 1 year before the start of MHT for current and previous MHT users, and as 1 year after the start of observation for subjects who had never received MHT. If any of the covariates required for analysis were missing or if there was a time interval of 1 year or more between the cohort entry date and the health examination date, these women were excluded from the analysis. Finally, a total of 19055 women aged between 45 and 60 years at baseline without preexisting stroke or underlying cardiovascular diseases were included in this study. The International Classification of Diseases (10th revision) codes for ischemic stroke and TIA are I63 and G45, respectively. The codes for the remaining comorbidities and outcomes are presented in Supplementary Table 1 (only online).

Exposure to MHT

Women were divided into groups of MHT never users, past users, and current users using a classical approach to examine the effects of MHT use on study outcomes.[18,19] Women who had been prescribed MHT for 6 months or who had used at least two MHT prescriptions within the past 6 months were classified as current users. Conversely, women who had been prescribed MHT for less than 6 months and had used fewer than two MHT prescriptions during the past 6 months were categorized as past users. Women with no MHT prescriptions were defined as never users. In South Korea, the maximum prescription period is limited to 6 months at tertiary hospitals and 3 months or less at primary and secondary medical institutions. Therefore, to ensure more accurate patient selection, both the prescription period and the number of prescriptions were taken into consideration together.

MHT were of different types, such as E-only MHT, E+P MHT, and tibolone. E-only MHT included oral CEE, oral estradiol (E2), and transdermal E2. E+P MHT included oral CEE plus progestin and oral E2 plus progestin. Generally, E-only MHT is restricted to women who have undergone a hysterectomy, whereas E+P MHT and tibolone are prescribed to women with a uterus. When two or more MHT types were administered, the regimen used for the longest period was chosen to classify the patients. The prescription codes for MHT are presented in Supplementary Table 1 (only online).

Statistical analysis

The characteristics of the groups defined by MHT use were compared using the chi-square test and one-way analysis of variance. We calculated the incidence rate (IR) per 1000 person-years and 95% confidence interval (CI) to compare the stroke incidence of MHT users to that of non-users. We obtained multivariable adjusted hazard ratios (HR)s and 95% CIs for new-onset stroke incidence between the groups defined by MHT use by using the Cox regression model. The health examination date with the smallest difference between the cohort entry date (date of first MHT prescription or study start date) and the health screening date was taken as the start of follow-up and followed until the first stroke event, death, or study end date (December 31, 2015), whichever occurred first. Model 1 was adjusted for age, body mass index, smoking status, alcohol consumption, and exercise. Model 2 was adjusted for Model 1 variables plus hypertension, diabetes, hypercholesterolemia, aspirin use, and statin use. Model 3 was adjusted for newly developed AF after MHT use in addition to the covariates used in Model 2. All covariates were based on the health screening date with the smallest difference between the health screening dates. We repeated the main analysis to assess the risk of stroke by MHT type among current MHT users and never users, and past MHT users and never users. All statistical analyses were performed using SAS Enterprise Guide® (SAS Institute Inc., Cary, NC, USA). All tests were two-tailed, with $p<0.05$ considered significant.

RESULTS

Characteristics of the study population and MHT treatment

Table 1 provides a summary of the demographic characteristics of the participants and the information related to the MHT they received. In the overall population, 16915 (88.77%) women had never undergone MHT, 1437 (7.54%) had previously undergone MHT, and 703 (3.69%) were currently using MHT. Within MHT ever users, 290 (13.55%) women were administered E-only, 712 (33.27%) women received E+P, and 1138 (53.18%) women were given tibolone.

At the baseline, the mean age was 51.12±4.29 years for MHT never users, which was significantly higher than that of MHT current users (48.27±3.18 years). The mean follow-up periods were 11.74±1.34 years, 7.86±2.53 years, and 5.84±2.89 years for MHT never, past, and current users, respectively. Among MHT users, the mean duration of MHT use was 3.71±2.28 years for current users and 2.55±1.50 years for past users. There were seven newly developed AF cases (1.00%) among the current users and 14 cases (0.97%) among the past users, which were not found to be significantly different when compared with the never users.

Stroke and MHT use

Table 2 presents the IRs of ischemic stroke among never, past, and current users of MHT. Among the 626 participants with stroke, 584 were never users, 19 were past users, and 23 were current users. The crude IRs of ischemic stroke were 2.94 per 1000 person-years, 1.68 per 1000 person-years, and 5.60 per 1000 person-years for never, past, and current users, respectively.

The HR of ischemic stroke was also significantly higher in current MHT users (HR of 2.98) with a 95% CI of 1.95–4.57 (p< 0.001) after adjusting for baseline characteristics such as age, body mass index, and lifestyle factors (model 1). Consistent results were observed after adjustment for underlying diseases and medications (model 2) and newly developed AF after MHT use (model 3). In past users, the stroke risk was not different from that in never users, even after adjusting for confounding factors.

Stroke in MHT current users

Table 3 shows the IRs and multivariable-adjusted HRs of ischemic stroke according to the MHT type for current users. The IRs of ischemic stroke in current users of E-only MHT, E+P MHT, and tibolone were significantly higher than those in never users. Meanwhile, the HRs of ischemic stroke in current users of E-only MHT (model 3, HR: 3.49, 95% CI: 1.12–10.90, p=0.032) and tibolone (model 3, HR: 3,52, 95% CI: 2.05–6.03, p<0.001) were significantly higher than that of never users, and the HR of E+P current users was higher than that of never users at the borderline level (model 3, HR: 2.20, 95% CI: 0.98–4.94, p=0.057).

A subgroup analysis was conducted based on estrogen type (Table 4). The HRs of ischemic stroke in current users of E2 alone (model 3, HR: 4.08, 95% CI: 1.31–12.77, p=0.016) and ti-

Table 1. Characteristics of Ischemic Stroke Cohort and Information of MHT Treatment

	Total (n=19055)	Never users (n=16915)	Past users (n=1437)	Current users (n=703)	*p* value
Mean follow-up period (yr)	11.23±2.13	11.74±1.34	7.86±2.53	5.84±2.89	<0.001
Age (yr)	50.87±4.26	51.12±4.29	49.26±3.47	48.27±3.18	<0.001
BMI (kg/m^2)	23.92±3.03	24.02±3.06	23.21±2.65	22.84±2.60	<0.001
Obesity	6325 (33.19)	5842 (34.54)	350 (24.36)	133 (18.92)	<0.001
Height (cm)	155.45±5.16	155.37±5.18	156.06±5.02	155.95±4.93	<0.001
Weight (kg)	57.81±7.86	58.01±7.95	56.53±6.93	55.57±6.83	<0.001
SBP (mm Hg)	122.90±17.35	123.29±17.55	120.08±15.73	119.28±14.47	<0.001
DBP (mm Hg)	76.84±11.50	77.11±11.61	74.94±10.60	74.34±9.79	<0.001
Total cholesterol (mg/dL)	203.86±60.45	204.34±62.72	200.87±38.42	198.55±36.35	0.002
HTN	7179 (37.68)	6599 (39.01)	411 (28.60)	169 (24.04)	<0.001
Diabetes	2291 (12.02)	2116 (12.51)	118 (8.21)	57 (8.11)	<0.001
HCL	2877 (15.10)	2599 (15.37)	197 (13.71)	81 (11.52)	0.006
Statin use at baseline	262 (1.37)	154 (0.91)	64 (4.45)	44 (6.26)	<0.001
Newly developed AF after baseline	221 (1.16)	200 (1.18)	14 (0.97)	7 (1.00)	0.715
MHT					<0.001
E-only	290 (1.52)	-	214 (14.89)	76 (10.81)	
E+P	712 (3.74)	-	470 (32.71)	242 (34.42)	
Tibolone	1138 (5.97)	-	753 (52.40)	385 (54.77)	
Never	16915 (88.77)	16915 (100)	-	-	
Mean duration of MHT use (yr)	2.50±1.98	-	2.55±1.50	3.71±2.28	<0.001
Smoking					0.001
Current	469 (2.46)	400 (2.36)	48 (3.34)	21 (2.99)	
Former	194 (1.02)	155 (0.92)	24 (1.67)	15 (2.13)	
Never	18392 (96.52)	16360 (96.72)	1365 (94.99)	667 (94.88)	
Alcohol consumption					<0.001
Rarely/never	17456 (91.61)	15687 (92.74)	1192 (82.95)	577 (82.08)	
1–2 drinks/week	1212 (6.36)	908 (5.37)	205 (14.27)	99 (14.08)	
3–4 drinks/week	241 (1.28)	191 (1.13)	30 (2.09)	20 (2.84)	
>5 drinks/week	146 (0.77)	129 (0.76)	10 (0.70)	7 (1.00)	
Exercise					<0.001
Rarely/never	11074 (58.12)	10255 (60.63)	593 (41.27)	226 (32.15)	
1–2 times/week	3994 (20.96)	3291 (19.46)	445 (30.97)	258 (36.70)	
3–4 times/week	2073 (10.88)	1644 (9.72)	270 (18.79)	159 (22.62)	
5–6 times/week	573 (3.01)	473 (2.80)	63 (4.38)	37 (5.26)	
7 times/week	1341 (7.04)	1252 (7.40)	66 (4.59)	23 (3.27)	

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; AF, atrial fibrillation; MHT, menopausal hormone therapy; E, estrogen; P, progestin; HCL, hypercholesterolemia.
Data are presented as mean±standard deviation or n (%).

https://doi.org/10.3349/ymj.2024.0053

Table 2. Risk of Ischemic Stroke According to MHT Use

	MHT use			
	Total (n=19055)	Never (n=16915)	Past (n=1437)	Current (n=703)
Number of ischemic stroke cases	626	584	19	23
Person-years	214040.53	198644.31	11288.53	4107.7
Incidence rate* (95% CI)	2.92 (2.70–3.16)	2.94 (2.71–3.19)	1.68 (1.07–2.64)	5.60 (3.73–8.42)
Age-adjusted incidence rate* (95% CI)	2.90 (2.89–2.92)	2.95 (2.93–2.96)	1.63 (1.6–1.67)	5.38 (5.27–5.5)
Age-adjusted HR (95% CI)		1.00 (reference)	0.71 (0.45–1.12)	2.75 (1.80–4.20)
			p=0.140	p<0.001
Model 1†			0.74 (0.47–1.18)	2.98 (1.95–4.57)
			p=0.202	p<0.001
Model 2‡			0.78 (0.49–1.24)	3.06 (2.00–4.69)
			p=0.301	p<0.001
Model 3§			0.79 (0.50–1.25)	3.09 (2.01–4.73)
			p=0.307	p<0.001

MHT, menopausal hormone therapy; CI, confidence interval; HR, hazard ratio.
*Per 1000 patient-years; †Model 1: Adjusted for age, body mass index, smoking status, alcohol consumption, and exercise; ‡Model 2: Additionally adjusted for hypertension, diabetes, hypercholesterolemia, aspirin use, and statin use; §Model 3: Additionally adjusted for newly developed atrial fibrillation after MHT use.

Table 3. Ischemic Stroke Risk According to the Type of MHT in Current Users

	MHT type (current users)				
	Total (n=17618)	None (n=16915)	E-only (n=76)	E+P (n=242)	Tibolone (n=385)
Number of ischemic stroke cases	607	584	3	6	14
Person-years	202752.01	198644.31	456.81	1480.35	2170.53
Incidence rate* (95% CI)	2.99 (2.77–3.24)	2.94 (2.71–3.19)	6.57 (2.13–20.29)	4.05 (1.82–9.01)	6.45 (3.83–10.87)
Age-adjusted incidence rate* (95% CI)	2.99 (2.97–3.00)	2.95 (2.93–2.96)	6.26 (5.89–6.63)	4.00 (3.83–4.17)	6.15 (5.98–6.32)
Age-adjusted HR (95% CI)		1.00 (reference)	3.17 (1.02–9.89)	2.04 (0.91–4.58)	3.07 (1.80–5.25)
			p=0.047	p=0.084	p<0.001
Model 1†			3.37 (1.08–10.52)	2.16 (0.96–4.86)	3.35 (1.95–5.73)
			p=0.037	p=0.063	p<0.001
Model 2‡			3.38 (1.08–10.58)	2.22 (1.00–5.00)	3.45 (2.01–5.91)
			p=0.036	p=0.054	p<0.001
Model 3§			3.49 (1.12–10.90)	2.20 (0.98–4.94)	3.52 (2.05–6.03)
			p=0.032	p=0.057	p<0.001

MHT, menopausal hormone therapy; E, estrogen; P, progestin; CI, confidence interval; HR, hazard ratio.
*Per 1000 patient-years; †Model 1: Adjusted for age, body mass index, smoking status, alcohol consumption, and exercise; ‡Model 2: Additionally adjusted for hypertension, diabetes, hypercholesterolemia, aspirin use, and statin use; §Model 3: Additionally adjusted for newly developed atrial fibrillation after MHT use.

bolone (model 3, HR: 3.52, 95% CI: 2.06–6.03, p<0.001) were higher than that of never users, and the HR of E2+P MHT users tended to be higher than that of never users (model 3, HR: 2.20, 95% CI: 0.98–4.94, p=0.057). Among those who were administered only estrogen, 13 women underwent CEE and none of them experienced an ischemic stroke, making it impossible to calculate the outcome.

Stroke in MHT past users

For past users, the risk of ischemic stroke was not significantly different from that of never users. Consistent results were obtained after analyses according to the type of estrogen and whether or not progestin was co-administered (Table 5 and Supplementary Table 2, only online). A limited number of women received transdermal E2 (n=3) and CEE+P (n=4), and no estimates were generated for stroke risk.

DISCUSSION

This study demonstrated that current MHT use was associated with an increased risk of ischemic stroke and TIA in women aged 45–60 years without underlying cardiovascular diseases. An increased risk of ischemic stroke was observed in E-only MHT and tibolone particularly. On the contrary, previous use of MHT was not associated with an increased risk of ischemic stroke.

The main finding of this study partially agrees with findings of previous studies. The results of the Nurses' Health Study showed an increased risk of stroke when MHT was used <10 years from

Table 4. Ischemic Stroke Risk in MHT Current Users According to Estrogen Type and Progestin Co-Treatment

	MHT regimen (current users)							
	Total (n=17618)	None (n=16915)	CEE (n=13)	E2 (n=63)	Trans-dermal E2 (n=0)	CEE+P (n=0)	E2+P (n=242)	Tibolone (n=385)
Number of ischemic stroke cases	607	584	0	3	-	-	6	14
Person-years	202752.01	198644.31	53.70	403.11			1480.35	2170.53
Incidence rate* (95% CI)	2.99 (2.77–3.24)	2.94 (2.71–3.19)	-	7.44 (2.41–22.98)			4.05 (1.82–9.01)	6.45 (3.83–10.87)
Age-adjusted incidence rate* (95% CI)	2.99 (2.97–3.00)	2.95 (2.93–2.96)		7.01 (6.60–7.43)			4.0 (3.83–4.17)	6.15 (5.98–6.32)
Age-adjusted HR (95% CI)		1.00 (reference)		3.63 (1.16–11.31)			2.04 (0.91–4.58)	3.07 (1.80–5.25)
				p=0.026			*p*=0.084	*p*<0.001
Model 1†				3.87 (1.24–12.09)			2.16 (0.96–4.86)	3.35 (1.95–5.73)
				p=0.020			*p*=0.063	*p*<0.001
Model 2‡				3.97 (1.27–12.41)			2.22 (0.99–5.00)	3.45 (2.01–5.91)
				p=0.018			*p*=0.054	*p*<0.001
Model 3§				4.08 (1.31–12.77)			2.20 (0.98–4.94)	3.52 (2.06–6.03)
				p=0.016			*p*=0.057	*p*<0.001

MHT, hormone replacement therapy; CEE, conjugated equine estrogen; E2, estradiol; P, progestin; CI, confidence interval; HR, hazard ratio.
*Per 1000 patient-years; †Model 1: Adjusted for age, body mass index, smoking status, alcohol consumption, and exercise; ‡Model 2: Additionally adjusted for hypertension, diabetes, hypercholesterolemia, aspirin use, and statin use; §Model 3: Additionally adjusted for newly developed atrial fibrillation after MHT use.

Table 5. Ischemic Stroke Risk According to the Type of MHT in Past Users

	MHT type (past users)				
	Total (n=18352)	None (n=16915)	E-only (n=214)	E+P (n=470)	Tibolone (n=753)
Number of ischemic stroke cases	603	584	1	6	12
Person-years	209932.84	198644.31	1798.43	3598.26	5891.84
Incidence rate* (95% CI)	2.87 (2.65–3.11)	2.94 (2.71–3.19)	0.56 (0.08–3.95)	1.67 (0.75–3.71)	2.04 (1.16–3.58)
Age-adjusted incidence rate* (95% CI)	2.86 (2.85–2.88)	2.95 (2.93–2.96)	0.5 (0.45–0.55)	1.72 (1.65–1.79)	1.91 (1.85–1.97)
Age-adjusted HR (95% CI)		1.00 (reference)	0.23 (0.03–1.61)	0.80 (0.36–1.78)	0.81 (0.46–1.44)
			p=0.1382	*p*=0.578	*p*=0.480
Model 1†			0.23 (0.03–1.66)	0.83 (0.37–1.86)	0.85 (0.48–1.51)
			p=0.150	*p*=0.649	*p*=0.583
Model 2‡			0.26 (0.04–1.85)	0.91 (0.41–2.05)	0.88 (0.50–1.56)
			p=0.179	*p*=0.824	*p*=0.661
Model 3§			0.26 (0.04–1.85)	0.92 (0.41–2.07)	0.88 (0.50–1.56)
			p=0.179	*p*=0.843	*p*=0.663

MHT, menopausal hormone therapy; E, estrogen; P, progestin; CI, confidence interval; HR, hazard ratio.
*Per 1000 patient-years; †Model 1: Adjusted for age, body mass index, smoking status, alcohol consumption, and exercise; ‡Model 2: Additionally adjusted for hypertension, diabetes, hypercholesterolemia, aspirin use, and statin use; §Model 3: Additionally adjusted for newly developed A-fib after MHT use.

menopause, which is consistent with the findings of the current research.[13] However, a pooled analysis of Swedish cohort studies reported different results, stating that when initiated <5 years, MHT was not associated with an increased risk of incident ischemic stroke after menopausal onset, regardless of the route of administration, type of MHT, active ingredient, and duration.[9]

The results of the WHI study revealed conflicting findings regarding the relationship between MHT and stroke risk. According to the latest report from the WHI, a subgroup analysis of women assigned to the MHT arm in their 50s found no significant increase in stroke risk, with a HR of 1.13 (95% CI: 0.73–1.76).[12] In contrast, an increased risk of stroke was observed in women who initiated MHT within 10 years of menopause, regardless of the type of MHT used, with an HR of 1.77 (95% CI: 1.05–2.98). In the WHI extension study, with a follow-up period of 10.7 years, the risk of stroke was no longer elevated during the post-intervention phase in the estrogen-only trial (HR: 0.89, 95% CI: 0.64–1.24). This finding is consistent with the results of the current study, which demonstrate no increased stroke risk among former MHT users.

Several factors could account for the discrepancy between the results of the current study and those of other studies, particularly the WHI study. These factors may include the differences in study design, composition of the study population, analysis methods, variations in the duration of MHT, specific types of

https://doi.org/10.3349/ymj.2024.0053

hormones used, and other potential confounding variables.

In addition to enrolling women who had not undergone MHT, the WHI study included participants who had previously undergone MHT, some of whom (past users) were randomly assigned to the placebo group. In the E-only trial, approximately 48.9% of the placebo group comprised women who were using or had previously used MHT.[7] Similarly, in the E+P trial, approximately 25.7% of the patients in the placebo group had a history of MHT administration.[6] These proportions highlight the complexity of the study population and can affect the interpretation of the results.

It is also essential to consider the intention-to-treat analysis conducted during the WHI trial. In this analysis, even if a stroke occurred after stopping the MHT following assignment to the MHT group, it was still counted as a stroke in the MHT group. This analysis method could have contributed to the differences observed between the results of the WHI and those of observational studies, including the current study.

Determining the appropriate follow-up period is a challenging aspect of research investigating the association between MHT and stroke. While long-term data have been published on MHT and CHD,[20-22] data on stroke are relatively limited. It is crucial to consider the duration of the follow-up period, as the findings may vary over time due to the lag time effect. Although WHI (1998) (E+P arm) reported no statistically significant differences between groups in the incidence of stroke during the first 2 years of the study,[3] women taking E+P MHT were observed to be at significantly higher risk of stroke after taking MHT for 3 or more years [at 3 years, relative risk (RR): 1.47, 95% CI: 1.02–2.11; at a mean of 5.6 years: HR: 1.44, 95% CI: 1.09–1.90].[6] In an observational study that included the WHI cohort,[23] the use of MHT within 5 years after menopause in women who had never used MHT before was found to significantly increase stroke risk, but this risk was observed only when MHT was taken for more than 5 years (CEE-only group, HR: 2.46, 95% CI: 1.29–4.70; and CEE+ MPA group, HR: 3.48, 95% CI: 1.36–8.96). These results indicate that a follow-up period of at least 5 years is necessary to observe the association between MHT and stroke risk.

As mentioned above, cardiovascular risk can be influenced by the formulation and dose. An increased risk of stroke with an increasing dose of estrogen was reported in the Nurses' Health Study.[13] In the Nurses' Health Study, a significantly increased stroke risk was demonstrated in women who were administered E-only MHT, whereas in women who used E+P MHT, the risk of stroke increased to a borderline level (RR: 1.22, 95% CI: 0.95–1.55). Similarly, the risk of ischemic stroke in the E+P MHT group appeared at a borderline level (HR: 2.20, 95% CI: 0.98–4.94, p=0.057) in the current study. Based on the results of these two studies, it appears that progestin may mitigate the action of estrogen; however, the biological effects of progestins on the cardiovascular system are not as well understood as those of estrogen. Another plausible explanation is that MHT with progestins influences the overall stroke risk by reducing the risk of AF. While only a limited number of studies have confirmed the association between MHT and AF, two large-scale studies have reported that E-only MHT is associated with an increased risk of AF, whereas E+P MHT does not increase AF risk.[24,25]

The variance in the results from the WHI and Swedish pooled analysis could potentially be attributed to the utilization of different MHT regimens among the women included in this study. The current study observed a higher proportion of women utilizing E2+P, instead of CEE+P, and tibolone compared to other studies. In the LIFT trial, which involved randomizing 4538 women aged between 60 and 85 years, the use of tibolone was associated with an increased risk of stroke (relative hazard: 2.19, 95% CI: 1.14–4.23, p=0.02).[26] Although the results are similar to those of this study, the LIFT trial focused on older women, making it inappropriate to directly compare with the current study, which involved only women who initiated MHT before the age of 60 years. In the LIBERATE trial, which included women younger than 60 years old, only five stroke cases were reported in both the tibolone and placebo groups (odds ratio: 0.99, 95% CI: 0.29–3.42), which contradicts the results of this study. However, it is important to note that the LIBERATE trial had a relatively short follow-up period, with a median duration of 3.1 years.[27]

In the current study, while the stroke risk showed a borderline increase in women currently receiving E+P MHT, a significant increase in stroke risk was observed among tibolone users. Progestins differ in their glucocorticoid, mineralocorticoid, and androgenic properties, and tibolone, in particular, metabolizes into compounds with estrogenic, progestogenic, and androgenic activity, showing affinity for both glucocorticoid and mineralocorticoid receptors. The co-administration of different types of progestins may significantly increase stroke risk or have no effect, depending on the specific progestin used. Further research is required to determine which progestin poses the lowest risk for stroke.

The strength of this study lies in its long-term follow-up of a large number of patients. This study included 19055 women who were followed up for a mean of 11.23 years. Among these participants, 2140 MHT users were followed up for a mean of 7.20 years. As MHT is typically recommended for use in women under the age of 60 years or within 10 years of menopause, the results of this study are more applicable to the target population compared to those of the WHI study, which included a substantial number of older women with various underlying health conditions.

Another strength of this study is the comprehensive consideration of various variables in the analyses. Specifically, AF was used as a correction variable and analyzed since it is one of the most important factors contributing to stroke risk. Although most studies have shown consistent results regarding the association between MHT and coronary artery disease, the link between MHT and stroke remains unclear. We hypothesized

that AF could influence variability in the results. Stroke and CHD share a common mechanism known as atherosclerosis. However, it is important to note that 20% of ischemic strokes are attributable to AF rather than atherosclerosis,[28,29] which may lead to different results in CHD. As mentioned previously, studies have reported that MHT increases the risk of incidental AF. As an increase in AF due to MHT could potentially increase the risk of stroke, this study considered these factors and conducted a thorough analysis.

Despite its intention, this study included a small number of women using various forms of MHT, which proved to be a limitation. There were only three women who had used transdermal E2 and four women who received the CEE+P regimen among the E+P MHT. Due to this limitation, the original purpose of the study, which aimed to evaluate whether the route of MHT administration affected the risk of stroke, could not be fully achieved.

Another limitation of this study is that the follow-up period for MHT current users was only 5.84±2.89 years. As mentioned above, based on previous studies, a follow-up period of at least 5 years seems to be necessary to observe the association between MHT and stroke risk due to the lag time effect. Given the scarcity of studies examining the effects of long-term MHT use for durations exceeding 10 years, it is currently difficult to determine the overall effect of MHT on stroke risk. Although the follow-up period of this study was 11.36±1.93 years, assessing the long-term risk of MHT for stroke was challenging due to the considerably shorter observation period for MHT ever users, excluding never users, with a mean follow-up of 7.27 years.

In conclusion, an increased risk of ischemic stroke and TIA was observed in women aged 45 to 60 years who are currently receiving MHT and have no underlying cardiovascular diseases. In particular, the risk was higher in women who were orally administered E-only MHT or tibolone. Therefore, for women who have not undergone hysterectomy, E+P MHT may be recommended rather than tibolone. Considering the risk was not sustained after stopping MHT, it is plausible that the potential benefits of prescribing MHT could outweigh the associated risks, particularly for women who have clear and well-defined medical indications for its use. These results were obtained from Korean women aged 45–60 years who did not use CEE-only or CEE+P agents, which are commonly used abroad. This should be taken into consideration when applying these findings in clinical practice.

ACKNOWLEDGEMENTS

This study was supported by the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (HI18C2047), and faculty research grant of Yonsei University College of Medicine (6-2022-0065).

AUTHOR CONTRIBUTIONS

Conceptualization: Jae Hoon Lee, Hyemin Park, Inha Lee, and Sihyun Cho. Data curation: Hyunji Park. Formal analysis: Hyunji Park and Changsoo Kim. Funding acquisition: Jong-Youn Kim. Investigation: Sung Pil Choo and Hyunji Park. Methodology: Kyung-Yul Lee. Project administration: Jae Hoon Lee and Jong-Youn Kim. Resources: Jong-Youn Kim. Software: Hyunji Park and Changsoo Kim. Supervision: Jong-Youn Kim. Validation: Jae Hoon Lee and Hyunji Park. Visualization: Hyemin Park. Writing—original draft: Sung Pil Choo and Jae Hoon Lee. Writing—review & editing: Sung Pil Choo and Jae Hoon Lee. Approval of final manuscript: all authors.

ORCID iDs

Sung Pil Choo https://orcid.org/0000-0002-7852-490X
Hyunji Park https://orcid.org/0000-0001-7793-554X
Hyemin Park https://orcid.org/0009-0006-3976-9871
Inha Lee https://orcid.org/0000-0003-4869-6281
Sihyun Cho https://orcid.org/0000-0003-2718-6645
Changsoo Kim https://orcid.org/0000-0002-5940-5649
Kyung-Yul Lee https://orcid.org/0000-0001-5585-7739
Jae Hoon Lee https://orcid.org/0000-0003-4223-1395
Jong-Youn Kim https://orcid.org/0000-0001-7040-8771

REFERENCES

1. Faubion SS, Crandall CJ, Davis L, El Khoudary SR, Hodis HN, Lobo RA, et al. The 2022 hormone therapy position statement of the North American Menopause Society. Menopause 2022;29:767-94.
2. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001;345:1243-9.
3. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-13.
4. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, et al. Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001;135:939-53.
5. Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA 2003;289:2673-84.
6. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
7. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-12.
8. Toh S, Hernández-Díaz S, Logan R, Rossouw JE, Hernán MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. Ann Intern Med 2010;152:211-7.
9. Carrasquilla GD, Frumento P, Berglund A, Borgfeldt C, Bottai M, Chiavenna C, et al. Postmenopausal hormone therapy and risk of

https://doi.org/10.3349/ymj.2024.0053

stroke: a pooled analysis of data from population-based cohort studies. PLoS Med 2017;14:e1002445.
10. Li C, Engström G, Hedblad B, Berglund G, Janzon L. Risk of stroke and hormone replacement therapy. A prospective cohort study. Maturitas 2006;54:11-8.
11. Løkkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Hundrup YA, et al. Increased risk of stroke in hypertensive women using hormone therapy: analyses based on the Danish Nurse Study. Arch Neurol 2003;60:1379-84.
12. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-77.
13. Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. Arch Intern Med 2008;168:861-6.
14. de Villiers TJ, Pines A, Panay N, Gambacciani M, Archer DF, Baber RJ, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 2013;16:316-37.
15. Seong SC, Kim YY, Khang YH, Park JH, Kang HJ, Lee H, et al. Data resource profile: the national health information database of the National Health Insurance Service in South Korea. Int J Epidemiol 2017;46:799-800.
16. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the national health insurance service–national sample cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46:e15.
17. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, et al. Background and data configuration process of a nationwide population-based study using the Korean National Health Insurance system. Diabetes Metab J 2014;38:395-403.
18. Helmond FA. Breast cancer and hormone-replacement therapy: the Million Women Study. Lancet 2003;362:1330-1.
19. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002;288:872-81.
20. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA 2011;305:1305-14.
21. Harman SM, Vittinghoff E, Brinton EA, Budoff MJ, Cedars MI, Lobo RA, et al. Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. Am J Med 2011;124:199-205.
22. Lobo RA, Pickar JH, Stevenson JC, Mack WJ, Hodis HN. Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. Atherosclerosis 2016;254:282-90.
23. Prentice RL, Manson JE, Langer RD, Anderson GL, Pettinger M, Jackson RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. Am J Epidemiol 2009;170:12-23.
24. Perez MV, Wang PJ, Larson JC, Virnig BA, Cochrane B, Curb JD, et al. Effects of postmenopausal hormone therapy on incident atrial fibrillation: the Women's Health Initiative randomized controlled trials. Circ Arrhythm Electrophysiol 2012;5:1108-16.
25. Wong JA, Rexrode KM, Sandhu RK, Moorthy MV, Conen D, Albert CM. Menopausal age, postmenopausal hormone therapy and incident atrial fibrillation. Heart 2017;103:1954-61.
26. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, et al. The effects of tibolone in older postmenopausal women. N Engl J Med 2008;359:697-708.
27. Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol 2009;10:135-46.
28. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology 2003;22:118-23.
29. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005;36:1115-9.