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Original Research

Association of menopausal hormone therapy with risk of cardiovascular disease in Korean women

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Abstract

Objective: To evaluate the association between various regimens and combinations of menopausal hormone therapy (MHT) and the risk of cardiovascular disease (CVD) in clinical practice.

Design: This was a population-based cohort study.

Methods: This population-based cohort study used data from the Health Insurance Review and Assessment Service. The data of women who reported entering menopause at ≥40 years of age with no history of CVD in the national health examination between 2011 and 2014 were extracted. A total of 134 298 pairs were included in the MHT and non-MHT groups after 1:1 propensity score matching. The participants were followed until December, 31, 2020.

Results: During a median follow-up of 7.9 (IQR 6.9-8.9) years, the incidences of CVD were 146 per 100 000 person/year and 179 per 100 000 person/year for the non-MHT and MHT groups, respectively. After adjusting for covariates, MHT use was associated with an increased CVD risk (hazard ratio [HR], 1.22 [1.14-1.31]) compared with the non-MHT group; the risk was based on an increased risk of stroke and coronary artery revascularization. Tibolone (HR, 1.38, [1.27-1.50]) was associated with increased CVD, but estrogen alone or combined estrogen/progestogen was not. There was no difference in CVD risk, regardless of the type of estrogen agent used. For combined estrogen/progestogen therapy, dydrogesterone was associated with reduced CVD risk.

Conclusions: There was an increased risk of CVD in MHT users. By regimen, tibolone use was associated with increased risk of CVD, whereas estrogen either alone or in combination with progestogen was not. There was no difference according to the type of estrogen. The type of progestogen seems to modify the results, since dydrogesterone was associated with reduced CVD risk.

Keywords: cardiovascular disease, cohort study, menopausal hormone therapy, menopause

Significance

This study highlights the increased risk of cardiovascular disease (CVD) associated with menopausal hormone therapy (MHT) use in Korean women. Tibolone, specifically, was associated with an increased CVD risk, whereas estrogen alone or combined with progestogen showed no significant risk increase. In more detailed combinations, interestingly, combined estrogen and dydrogesterone were associated with a reduced CVD risk. These findings provide crucial insights for clinicians in selecting MHT regimens while considering long-term cardiovascular health, emphasizing the importance of tailored treatment approaches based on regimen-specific outcomes. Further mechanistic and prospective studies are warranted to validate these results.

Introduction

Cardiovascular disease (CVD) remains a leading cause of death worldwide, accounting for 35% of total deaths in women in 2019.[1] Despite menopausal hormone therapy (MHT) being the most efficient approach for managing menopausal vasomotor symptoms,[2] its clinical use is frequently constrained owing to apprehension about CVD risks. However, the effect of MHT on cardiovascular outcomes in postmenopausal women remains unclear.

The effect of MHT on CVD in women has been extensively studied, and the findings have evolved over time. Early large-scale randomized controlled studies raised concerns about the risks associated with MHT.[3,4] The final analysis of Women's Health Initiative (WHI) demonstrated that the risk of coronary heart disease was not significant in women taking oral combined estrogen and progestin therapy and suggested a "timing hypothesis" proposing that women who started MHT within 10 years postmenopause tended to have

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a reduced risk of CVD, whereas women who started MHT more than 20 years postmenopause had a significantly increased risk of CVD.[5] A recent meta-analysis comprising 19 randomized controlled trials comparing MHT to a placebo presented risk data indicating an increased risk of stroke and venous thromboembolism associated with MHT use.[6] However, starting MHT within the first 10 years of menopause led to a lower incidence of coronary heart disease, supporting the timing hypothesis.[6] The timing hypothesis was subsequently validated as a treatment strategy through the further randomized studies,[7,8] and domestic and international guidelines recommend starting MHT as soon as possible after menopause.[9,10] An analysis that used the Danish national register data found that continuous combined therapy was associated with a higher risk of myocardial infarction (MI), whereas transdermal route of delivery may reduce the risk of MI, suggesting that MHT regimen or route of application may influence the risk of MI.[11] Unresolved queries remain regarding the effect of various regimens according to estrogen types, progestogen types, and their combinations in MHT.

This study aimed to evaluate the risk of CVD according to MHT use in postmenopausal women using Korean nationwide cohort data, especially and specifically investigated the influence of various regimens.

Methods

Data sources

The National Health Insurance Service (NHIS), a mandatory national health insurance program provided by the South Korean government, is a single-payer healthcare system.[12] The Korean Health Insurance Review and Assessment Agency (HIRA) is a national organization that determines the appropriateness of medical expenses billed by healthcare providers to NHIS in South Korea, and it maintains a comprehensive database of all national health insurance use data in South Korea. This database contains information related to the entire Korean population. Diagnoses within the database were encoded in accordance with the Tenth Revision of the International Classification of Diseases (ICD-10) codes. This study employed a population-based retrospective cohort design using the Korean National Health Claims database from 2007 to 2020 provided by HIRA.

Study population

This study enrolled women aged 40 years or older who had their initial visit to a healthcare provider for menopause (N95.1: menopausal and female climacteric states) from January, 1, 2011, to December, 31, 2014. A visual representation of the patient selection process is shown in Figure 1. For the MHT group, we included women aged 40 years or older who received MHT for the first time between January, 1, 2011, and December, 31, 2014. To ensure consistency, participants who had used MHT for <6 months were excluded. For the non-MHT group, we selected women aged 40 years or older who sought healthcare between January, 1, 2011, and December, 31, 2014, for menopausal-related concerns. Among them, however, participants who were prescribed MHT at any time were excluded. Women with preexisting cancer (any Cxx code), anemia (codes D62–64), except for iron deficiency anemia (code D50), CVD (codes I11, I13, I21-25, I60-64, I42, and I50), previous prescription of antithrombotic agents, or those who underwent cardiovascular procedures before day 180 of study entry were excluded. Women who changed the type of MHT during the study period were also excluded. Propensity score matching was conducted at a 1:1 ratio for age, year of enrollment, socioeconomic status (SES), residential area, Charlson comorbidity index (CCI), hypertension, diabetes mellitus, dyslipidemia, uterine fibroids, endometriosis, hysterectomy, and adnexal surgery in both groups.

Outcomes

The primary outcome was incidental CVD, defined as first hospitalization or death due to MI, coronary artery revascularization, or stroke. The individual components of the primary outcome were also evaluated as secondary outcomes. Myocardial infarction was defined as a record of hospitalization with diagnostic codes I21-23 and receipt of an intervention. Stroke was defined as a record of hemorrhagic stroke (codes I60-62) or ischemic stroke (codes I63-64) during an inpatient visit. Coronary artery revascularization was defined as hospitalized women receiving an intervention (percutaneous intravascular installation of metallic stent, percutaneous transcatheter placement of intracoronary stent, percutaneous thrombus removal, percutaneous transluminal angioplasty, percutaneous transluminal coronary atherectomy, percutaneous transluminal coronary angioplasty). We only considered hospitalization or death with the above diagnoses as primary diagnoses for hospitalization or primary causes of death. The event date was set as the date when CVD was first confirmed, and the last observation date (censoring) was the last recorded date, including death, for any reason identified in the health insurance data. Participants were followed up until death due to any cause or the end of the study (December, 31, 2020).

Exposure

The analysis incorporated various MHT treatments, namely tibolone and estrogen-only treatments, eg, conjugated equine estrogen (CEE), estradiol valerate (EV), estradiol hemihydrate (EH), and transdermal estradiol. Additionally, MHT includes combined estrogen/progestogen formulations containing drospirenone (EH/DRSP), norethisterone acetate (EH/NETA), dydrogesterone (EH/DYD), cyproterone acetate (EV/CPA), medroxyprogesterone acetate (EV/MPA), and norethisterone (EV/NETA). For subgroup analysis, MHT was further categorized as tibolone, combined estrogen/progestogen formulations (EH/DRSP, EH/NETA, EH/DYD, EV/CPA, EV/MPA, EV/NETA, CEE with MPA or NETA or DYD, EV with MPA or NETA or DYD, and EH with MPA or NETA or DYD) and estrogen-only treatments (CEE, EV, EH, and transdermal estradiol). Further, the classification of MHT considered the oral administration of estrogenic or progestogenic components.

Variables

Data regarding age, SES, and residential location were obtained from the health insurance records. SES was categorized as low-quality (medical aid) or mid- to high-quality (no medical aid). Charlson comorbidity indices were computed on the basis of ICD-10 codes spanning from 1 year before study commencement until the date of study participation.[13] The presence of uterine fibroids, endometriosis, diabetes mellitus,

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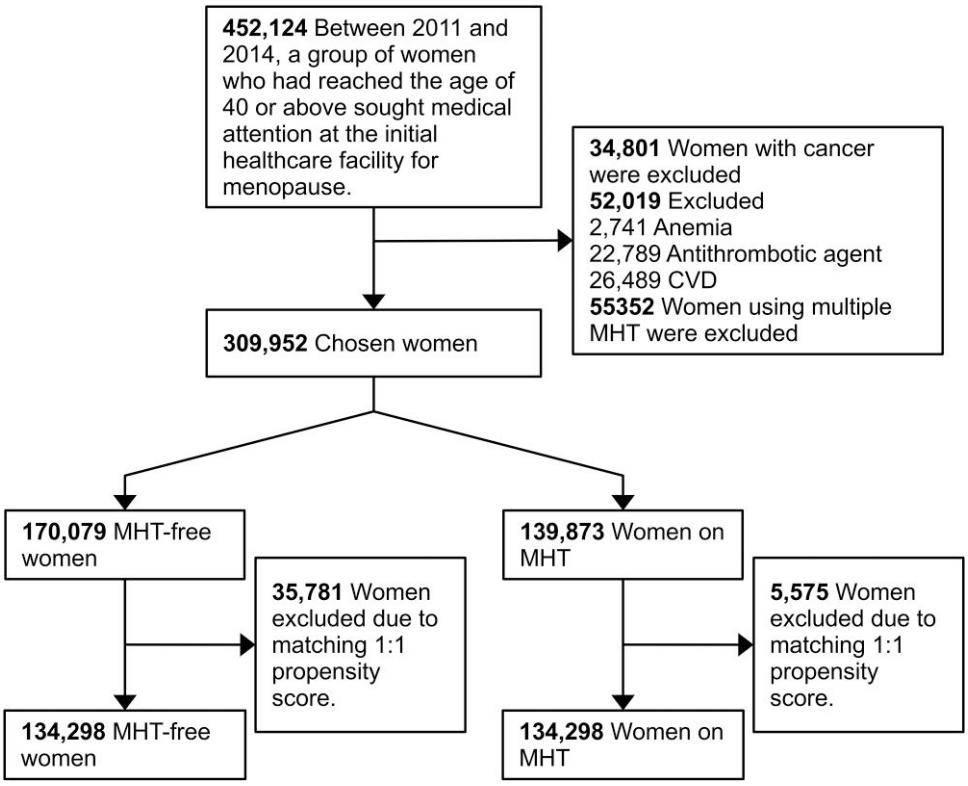


Figure 1. Flowchart of the selection of patients in the MHT and non-MHT groups from HIRA data. HIRA, Health Insurance Review and Assessment Service; MHT, menopausal hormone therapy.

dyslipidemia, and hypertension was established when the corresponding ICD-10 codes were confirmed on 3 or more occasions. Information about prior hysterectomy and adnexal surgery was obtained using surgical codes.

Statistical analysis

Categorical variables are presented as numbers and percentages, whereas continuous variables are reported as medians (25th and 75th percentiles). Before propensity score matching, categorical analyses were conducted using the χ^2 test, and continuous variables were analyzed using either the *t*-test (parametric) or Mann–Whitney U test (non-parametric). Following propensity score matching, the Cochran–Mantel–Haenszel test was used to analyze categorical variables, whereas the paired *t*-test (parametric) or Wilcoxon signed-rank test (non-parametric) was employed to analyze continuous variables. The standardized mean difference was calculated to determine the difference between the 2 groups and evaluate how well they were matched. To determine the incidence of CVD, the number of CVD cases was divided by 100 000 person-years. We used extended Cox proportional hazards regression models with time-dependent covariates to examine the association between MHT and the CVD risk, and we performed a Schoenfeld residual test to assess the validity of the Cox proportional hazards model. The start date of MHT was defined as the first day on which the initial MHT prescription was administered. In the non-MHT group, we assigned the start date as that on which the first menopausal diagnosis code (N95.1) was confirmed. To minimize immortality bias, we calculated and applied the time from the first diagnosis of menopause to the first prescription of MHT in the MHT and non-MHT groups. The Cochran–Armitage test for trends was used to assess changes in MHT use over time. There were no missing data regarding the baseline cohort characteristics because HIRA has national data linked to the resident registration numbers given by the state to all citizens. All tests were two-sided, and the results were considered statistically significant at $P < .05$. Statistical analyses were performed using R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Overall, 452 124 postmenopausal women aged 40 years were identified between 2011 and 2014, and 134 298 participants were assigned to the MHT and non-MHT group. The baseline demographic and clinical characteristics of both groups before and after propensity score matching are summarized in Table S1 and Table 1, respectively. After propensity score matching, none of the included variables had a standardized mean difference exceeding 0.2. Participants' median age was 50 (47-53) years, and >95% of participants were in their 40s or 50s. The median duration of menopausal hormone use in the MHT group was 22 (10-51) months, with 86 303 (64.3%) MHT users using it for <3 years (Table S2).

Cardiovascular outcomes according to MHT use

During a median follow-up of 7.9 (6.9-8.9) years, the incidences of CVD were 146 per 100 000 person/year and 179 per 100 000 person/year in the non-MHT and MHT groups, respectively. The incidence of CVD is given in Table S3. In Cox proportional hazards analysis with time-dependent

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Table 1. Comparison of characteristics of women between the post-propensity score-matched MHT and non-MHT groups.

Characteristics	Participants, no. (%)			*P*-value	Standardized mean difference	Missing (%)
	Total ($n = 268\,596$)	Non-MHT ($n = 134\,298$)	MHT ($n = 134\,298$)			
Follow-up period, years	7.9 (6.9-8.9)	7.9 (6.8-8.9)	8 (6.9-8.9)	.848	0.062	NA
Age, median (IQR), years	50 (47-53)	50 (47-54)	50 (48-53)	.007	0.072	NA
Age at inclusion, years				<.001	0.005	0
40-49	114 653 (42.7)	57 443 (42.8)	57 210 (42.6)			
50-59	142 756 (53.1)	71 223 (53)	71 533 (53.3)			
60-69	10 998 (4.1)	5539 (4.1)	5459 (4.1)			
≥70	189 (0.1)	93 (0.1)	96 (0.1)			
Year at inclusion				<.001	0.005	0
2011	72 027 (26.8)	36 146 (26.9)	35 881 (26.7)			
2012	71 723 (26.7)	35 765 (26.6)	35 958 (26.8)			
2013	65 615 (31.3)	32 817 (31.3)	32 798 (31.3)			
2014	59 231 (22.1)	29 570 (22)	29 661 (22.1)			
SES				<.001	0.005	0
Mid–high SES	262 090 (97.6)	131 092 (97.6)	130 998 (97.5)			
Low SES	6506 (2.4)	3206 (2.4)	3300 (2.5)			
Region				.096	0.006	0
Urban area	131 722 (49)	66 076 (49.2)	65 646 (48.9)			
Rural area	136 874 (51)	68 222 (50.8)	68 652 (51.1)			
CCI				<.001	0.019	0
0	194 571 (72.4)	97 786 (72.8)	96 785 (72.1)			
1	46 942 (17.5)	23 015 (17.1)	23 927 (17.8)			
≥2	27 083 (10.1)	13 497 (10.1)	13 586 (10.1)			
Hypertension	46 510 (17.3)	23 077 (17.2)	23 433 (17.4)	<.001	0.007	0
Diabetes	25 145 (9.4)	12 435 (9.3)	12 710 (9.5)	<.001	0.007	0
Dyslipidemia	66 202 (24.6)	32 485 (24.2)	33 717 (25.1)	<.001	0.021	0
Uterine fibroids	41 966 (15.6)	21 195 (15.8)	20 771 (15.5)	.013	0.009	0
Endometriosis	11 069 (4.1)	5456 (4.1)	5613 (4.2)	<.001	0.006	0
Previous hysterectomy	10 541 (3.9)	5243 (3.9)	5298 (3.9)	.002	0.002	0
Previous adnexal surgery	5193 (1.9)	2557 (1.9)	2636 (2)	<.001	0.004	0

Categorical variables are presented as number (%), whereas continuous variables are presented as median (25th and 75th percentiles).
CCI, Charlson comorbidity index; IQR, inter-quartile range; MHT, menopausal hormone therapy; SES, socioeconomic status.

covariates, MHT use was associated with an increased CVD risk (hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.14-1.31) (Table 2 and Figure 2A). The incidence of MI did not differ between the groups (HR, 1.15; 95% CI, 0.89-1.50), whereas the occurrence of stroke (HR, 1.28; 95% CI, 1.16-1.41) and coronary artery revascularization (HR, 1.22; 95% CI, 1.08-1.39) was significantly higher in the MHT group than in the non-MHT group (Table 2).

Effect of the MHT regimen on cardiovascular risk

In subgroup analyses stratified by the MHT regimen, tibolone (HR, 1.38; 95% CI, 1.27-1.50) was associated with an increased CVD risk, but neither combined estrogen/progestogen (HR, 1.09; 95% CI, 1.00-1.19) nor estrogen alone (HR, 1.11; 95% CI, 0.94-1.30) showed a difference in the CVD risk (Table 3 and Figure 2B). None of the estrogenic agents were associated with the CVD risk (Figure S1). However, DYD was associated with a reduced CVD risk (HR, 0.74; 95% CI, 0.56-0.98), whereas the other progestogens were not (Figure S1).

Sensitivity analysis

The risk of CVD decreased with an increasing duration of MHT use ($P < .001$) (Table 4). Women who used MHT for ≥6 years had no difference in the CVD risk compared with those who did not use MHT (HR, 1.19; 95% CI, 0.96-1.48). Menopausal hormone therapy was associated with the CVD risk in those aged 40s (HR, 1.19; 95% CI, 1.05-1.34) and 50s (HR, 1.24; 95% CI, 1.13-1.36), but not in those aged ≥60 years (Table S4). In the sensitivity test that included only postmenopausal women with a CCI score of 0, MHT was associated with an increased risk of CVD, consistent with the main results (HR, 1.23; 95% CI, 1.14-1.34).

Discussion

In this analysis from a nationwide cohort study using the HIRA, we found that women who received MHT had a higher risk of CVD compared with those who did not receive MHT. Regarding the MHT regimen, tibolone was significantly associated with an increased risk of CVD, whereas women who received estrogen either alone or in combination with progestogen did not show an increased risk. There was no difference in the CVD risk, regardless of the type of estrogen used. For combined estrogen and progestogen therapy, DYD was associated with a reduced risk of CVD.

The increased incidence of CVD in postmenopausal women has prompted extensive research on the potential cardiovascular benefits of MHT through observational and randomized studies. However, the conclusions from these studies are diverse, reflecting varied MHT effects based on regimens and age groups. The influential WHI study, encompassing estrogen-only and estrogen plus progestin arms, revealed MHT increased the risk of stroke and venous thromboembolism, with neutral effect on the risk of coronary heart disease.[4,5] However, the regimen (CEE 0.625 mg/day plus MPA 2.5 mg/day) in the WHI study is currently used in most countries and majority of WHI participants

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Table 2. Incidence and HRs of cardiovascular outcomes in relation to MHT.

Cardiovascular outcomes	Case/person-years (case/100 000 person-years)		Crude HR (95% CI)	*P*-value
	Non-MHT	MHT		
Cardiovascular disease	1660/1 137 002 (146)	1713/958 784 (179)	1.22 (1.14-1.31)	<.001
Myocardial infarction	112/1 137 002 (10)	109/958 784 (11)	1.15 (0.89-1.50)	.291
Stroke	1248/1 137 002 (110)	1290/958 784 (135)	1.22 (1.13-1.32)	<.001
Hemorrhagic stroke	465/1 137 002 (41)	448/958 784 (47)	1.14 (1.00-1.30)	.053
Ischemic stroke	823/1 137 002 (72)	889/958 784 (93)	1.28 (1.16-1.41)	<.001
Coronary revascularization	466/1 137 002 (41)	479/958 784 (50)	1.22 (1.08-1.39)	.002

CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy.

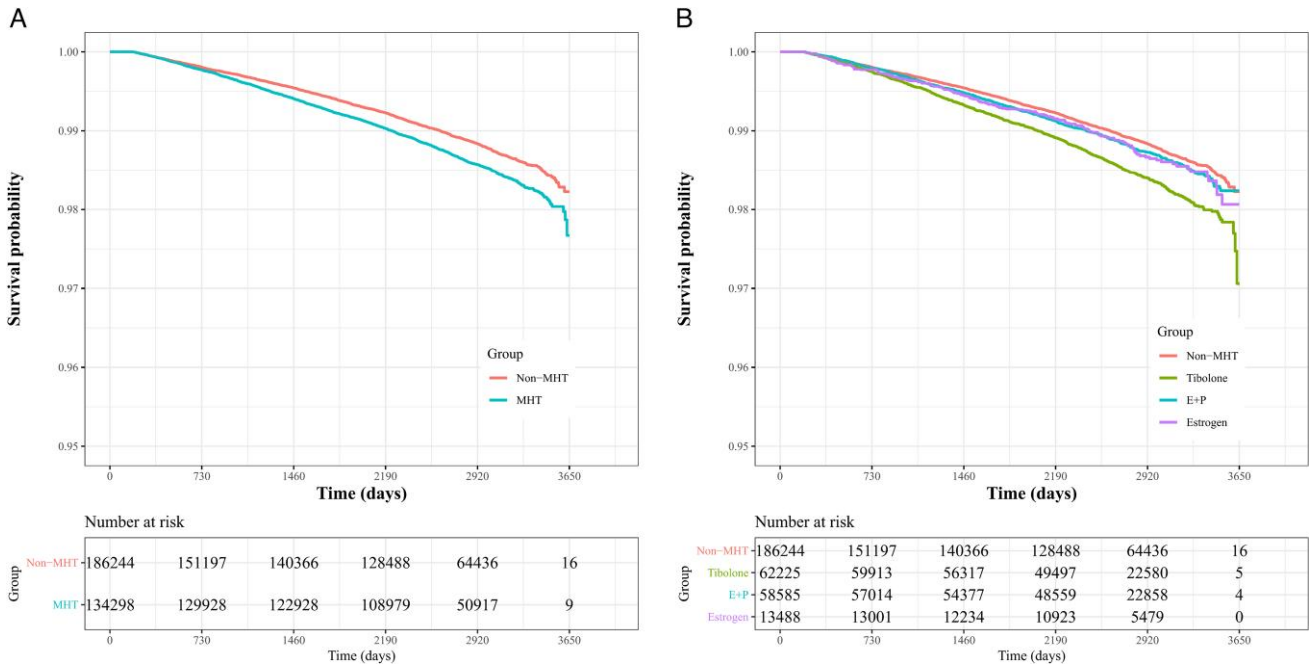


Figure 2. Assessing CVD risk with MHT using a Kaplan–Meier plot. (A) Kaplan–Meier plot of MHT users versus nonusers (log-rank test: *P*-value <.001). (B) Kaplan–Meier plot by classification on MHT (log-rank test: *P*-value <.001). MHT, menopausal hormone therapy.

were over 60 years of age. These limitations of the WHI study, including the outdated regimen, older participant age, high loss to follow-up, and failed to adequately account for missing outcomes, prompted further investigation.[14] In the Danish Nurse Study, MHT users, particularly hypertensive women, showed an increased stroke risk, emphasizing cautious administration in this population.[15] However, the study omitted an analysis based on the MHT regimens. Another Danish study found no overall increase in the MI risk with MHT.[11] When examined by regimen, it was found that while unopposed estrogen, cyclical combination therapy, or tibolone did not increase the risk, continuous combination regimens did. On the other hand, the risk of MI decreased with transdermal unopposed estrogen.[7] On the basis of previous studies, our study evaluated various MHT regimens and combinations that have recently been used in clinical practice, and found that MHT users had a higher risk of CVD than non-MHT users, showing a significant difference only in tibolone users. Risk was based on an increased risk of stroke and coronary artery revascularization.

Concerning regimen, tibolone was associated with a 38% increased risk of CVD, which was comparable to previous findings from a randomized controlled trial[16] and a large epidemiologic study.[17] The pathophysiologic links that underlie the increased occurrence of CVD events with the use of tibolone remain uncertain. The use of tibolone results in elevated serum C-reactive protein levels,[18] which may modulate atherosclerosis. Although tibolone decreases triglyceride and low-density lipoprotein cholesterol levels, it is also associated with a reduction in high-density lipoprotein cholesterol levels.[19] Treatment with tibolone is also accompanied by an increase in plasminogen levels.[18] These findings may be the plausible mechanisms by which tibolone can affect the risk of CVD. Although combined estrogen/progestogen and estrogen levels alone were not statistically significant, they tended to increase the incidence of CVD. There was no difference in the CVD risk, regardless of the type of estrogen used. Limited data exist on the CVD risk related to various progestogen types; however, a meta-analysis demonstrated that micronized progesterone (MP) has a neutral impact on the cardiovascular system.[20] Our results showed that combined estrogen and progestogen, including NETA, MPA, DRSP, CPA, and MP, did not have a significant impact on CVD risk. Interestingly, estrogen plus DYD decreased the CVD risk. There are limited clinical data on the effect of DYD on the cardiovascular system; however, previous experiments have shown that DYD, unlike other progestogens, is largely neutral in terms of blood pressure or surrogate markers

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Table 3. Incidence and HRs of the primary outcome in relation to the MHT regimen.

MHT regimen	No.(%) of CVD events	Case/person-years (case/100 000 person-years)	Crude HR (95% CI)[a]
Total	1713/134 298 (1.3)	1713/958 784 (179)	1.22 (1.14-1.31)
Category 1			
Tibolone	879/62 225 (1.4)	879/437 871 (201)	1.38 (1.27-1.50)
E + *P*	677/58 585 (1.2)	677/424 149 (160)	1.09 (1.00-1.19)
Estrogen alone	157/13 488 (1.2)	157/96 764 (162)	1.11 (0.94-1.30)
Category 2			
Tibolone	879/62 225 (1.4)	879/437 871 (201)	1.38 (1.27-1.50)
EH/DRSP	367/32 031 (1.1)	367/229 887 (160)	1.09 (0.98-1.22)
EH/NETA	60/3931 (1.5)	60/29 169 (206)	1.39 (1.08-1.80)
EH/DYD	53/5974 (0.9)	53/41 992 (126)	0.87 (0.66-1.14)
EV/CPA	158/14 339 (1.1)	158/106 428 (148)	1.01 (0.86-1.19)
EV/MPA	15/854 (1.8)	15/6467 (232)	1.56 (0.94-2.60)
EV/NETA	3/112 (2.7)	3/878 (342)	2.31 (0.74-7.16)
CEE	15/1719 (0.9)	15/11 084 (135)	0.94 (0.57-1.57)
EV	136/11 397 (1.2)	136/82 774 (164)	1.12 (0.94-1.33)
EH	3/167 (1.8)	3/1347 (223)	1.45 (0.47-4.50)
CEE/MP	4/352 (1.1)	4/2375 (168)	1.18 (0.44-3.14)
CEE/MPA	0/98 (0)	0/581 (0)	NA
CEE/DYD	0/28 (0)	0/184 (0)	NA
EV/MP	4/393 (1)	4/2819 (142)	0.97 (0.36-2.57)
EV/MPA	5/257 (1.9)	5/1817 (275)	1.89 (0.78-4.54)
EV/DYD	0/26 (0)	0/211 (0)	NA
EH/MP	8/184 (4.3)	8/1295 (618)	4.20 (2.10-8.41)
EH/MPA	0/5 (0)	0/38 (0)	NA
EH/DYD	0/1 (0)	0/8 (0)	NA
TE	3/205 (1.5)	3/1559 (192)	1.28 (0.41-3.97)

[a]Values were obtained by using the non-MHT groups as the reference.
CEE, conjugated equine estrogen; CEPM, combined estrogen plus progestin by the manufacturer; CEPP, combined estrogen plus progestin by the physician; CI, confidence interval; CPA, cyproterone acetate; DRSP, drospirenone; DYD, dydrogesterone; EH, estradiol hemihydrate; EV, estradiol valerate; HR, hazard ratio; MHT, menopausal hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone acetate; NA, not available; NETA, norethisterone acetate; TE, transdermal estrogen.

of vascular function.[21] Additionally, DYD has a neutral effect on hemostasis. Further research is required to assess the safety of using a combination of estrogen and DYD in terms of cardiovascular health in clinical practice. Moreover, its suitability as an option for women at a high risk of CVD warrants further investigation.

The duration of MHT may act as an important effect modifier of the influence of MHT on CVD. According to the Danish national register data, the risk of MI gradually decreased in women who used MHT for a longer period than in those who never used MHT.[11] Additionally, the study identified an increase in MI incidence with longer systemic MHT use in the younger age group compared with the older age group, indicating that age might be a factor influencing the effect of MHT duration. In this study, although the significance of the increase in the CVD risk diminished with an extended duration of MHT use, the trend of increased CVD persisted. However, careful consideration is needed when interpreting this correlation as there could be cases of early MHT discontinuation due to the occurrence of CVD events. The duration between the initiation or cessation of MHT and the onset of CVD may also be a crucial factor; however, our study did not address this issue. Future studies with further adjustments and analyses of these effect modifiers are needed to clarify concerns regarding the long-term safety related to MHT.

The *post hoc* analysis of the WHI study and a meta-analysis including the WHI study suggested that starting MHT before 60 years of age or within 10 years of menopause may have a beneficial effect on coronary heart disease without increasing the risk of stroke.[5,6] Further randomized trials clearly demonstrated a cardio-protective effect of MHT, when it is initiated at a younger age of 45-58 years or within 6 years postmenopause.[7,8] On the basis of these findings, both the National Institute of Healthcare Excellence guidelines and the Korean guidelines on menopausal management state that initiating MHT before 60 years of age or within 10 years of menopausal onset may not increase the risk of stroke and potentially reduce the incidence of coronary heart disease.[9,10] However, the Danish national register data demonstrated contradictory results, revealing an elevated risk of MI in young women in their 50s, with the highest incidence observed in those who were prescribed continuous MHT regimens across all age groups.[11] Moreover, findings from the Nurse's Health Study indicated an elevated risk of stroke regardless of the timing of MHT initiation.[22] In addition, there are few studies exploring whether the timing hypothesis applies to tibolone, which constitutes a significant portion of our research. Here, MHT users in the young age group in their 40s-50s had a significantly higher CVD risk than non-MHT users, and our results raise concerns about the suggestion of prescribing MHT from younger ages according to the timing hypothesis.

This study had several limitations. First, although it included a large population from the national registration data and a long follow-up duration, it was a retrospective observational study. Second, because the study population was ethnically homogeneous (Koreans), caution is needed when generalizing the results to other ethnic groups with distinct genetic factors and lifestyles according to race and location. In addition, tibolone is the most commonly prescribed single agent in Korea, accounting for 46% of total MHT usage. The results should be interpreted in that context. Third, research using administrative databases may have resulted in coding errors. Minimizing this problem involved

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Table 4. Incidence and HRs of the primary outcome by the duration of MHT.

MHT regimen	MHT duration, years								
	<3			3-5.9			≥6		
	Case/person-years (case/100 000 person-years)	HR (95% CI)	*P*-value	Case/person-years (case/100 000 person-years)	HR (95% CI)	*P*-value	Case/person-years (case/100 000 person-years)	HR (95% CI)	*P*-value
Non-MHT	1660/1 137 002 (146)	1	NA	1165/1 102 507 (106)	1	NA	542/1 023 411 (53)	1	NA
MHT total	1159/597 522 (194)	1.33 (1.24-1.44)	<.001	250/208 104 (120)	1.19 (1.04-1.36)	.014	98/150 006 (65)	1.19 (0.96-1.48)	.110
Category 1									
Tibolone	550/265 302 (207)	1.43 (1.30-1.58)	<.001	141/99 033 (142)	1.42 (1.19-1.69)	<.001	53/71 864 (74)	1.35 (1.02-1.79)	.038
E + *P*	501/272 125 (184)	1.26 (1.14-1.39)	<.001	89/88 722 (100)	0.98 (0.79-1.22)	.883	32/62 038 (52)	0.95 (0.67-1.36)	.782
Estrogen alone	108/60 095 (180)	1.23 (1.01-1.50)	<.001	20/20 350 (98)	.96 (0.62-1.50)	.871	13/16 105 (81)	1.41 (0.81-2.44)	.225

CI, confidence interval; CVD, cardiovascular disease; E, estrogen; HR, hazard ratio; MHT, menopausal hormone therapy; NA, not available; P, progesterone.

the application of definitions that had been validated in previous studies conducted using the Korean NHIS database.[23,24] Fourth, women using multiple types of MHT were excluded from this study, which may have influenced the results. Fifth, propensity score matching was used to address the balance between participants with and without MHT use. Nevertheless, the potential for unmeasured residual confounding factors such as smoking status, body mass index, or family history of CVD persists due to data limitations. Sixth, analysis according to different dosages of various MHT preparations route of administration was not performed in this study. Seventh, among the women who used estrogen alone, those who used levonorgestrel-releasing intrauterine system for MHT could not be analyzed in this study because such cases are not eligible for insurance coverage in Korea. Lastly, the study did not examine the reasons for initiating MHT or the specific indications for its use.

In this nationwide cohort study of Korean women, MHT use was associated with an increased risk of CVD compared with non-MHT use. Regarding the regimen of MHT, tibolone showed a significant correlation with CVD, while estrogen either alone or in combination with progestogen did not. The risk did not differ with the type of estrogen. In combined estrogen and progestogen therapy, however, DYD was associated with a reduced risk of CVD. Our findings underscore the need for healthcare providers to consider patients' future risk of CVD when selecting a regimen for MHT.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Author's contributions

Jin-Sung Yuk (Conceptualization [equal], Data curation [lead], Formal analysis [lead], Progject administration [lead], Methodology [equal], Visualization [lead], Writing—original draft [equal], Writing—review & editing [equal]), Gwang Sil Kim (Funding acquisition [lead], Resources [equal]), Dong-Gil Kim (Resources [equal]), Young Sup Byun (Resources [equal], Software [lead]), Myoung-Hwan Kim (Resources [equal]), Sang-Hee Yoon (Resources [equal]), Gwan Hee Han (Resources [equal]), and Byung Gyu Kim (Conceptualization [equal], Supervision [lead], Investigation [lead], Methodology [equal], Validation [lead], Writing—original draft [equal], Writing—review & editing [lead]).

J.-S.Y. had full access to all of the data in the study, took responsibility for the integrity of the data and the accuracy of the data analysis, and was involved in acquisition, analysis, or interpretation of data. J.-S.Y. and B.G.K. contributed to the concept and design and drafted the manuscript. All authors

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were involved in the critical revision of the manuscript for important intellectual content

Conflict of interest: All authors declare no conflict of interest.

Data availability

Per Health Insurance Review and Assessment Service's privacy policy, raw data cannot be provided.

Ethics statement

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local institutional review board (approval number: SGPAIK-2022-02-020). Informed consent was not required because the datasets did not contain any personal identifiable information. Data analysis was conducted on the HIRA server only. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

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