Hypertension

ORIGINAL ARTICLE

Association Between the Route of Administration and Formulation of Estrogen Therapy and Hypertension Risk in Postmenopausal Women: A Prospective Population-Based Study

Cindy Z. Kalenga, Amy Metcalfe, Magali Robert, Kara A. Nerenberg, Jennifer M. MacRae, Sofia B. Ahmed

BACKGROUND: Hypertension is the leading global cause of cardiovascular disease and premature mortality in women. The effects of postmenopausal hormone therapy (HT) on blood pressure are uncertain but may be related to route of estrogen administration and formulation of estrogen. We sought to determine the association between route of administration and formulation of estrogen HT and hypertension risk in postmenopausal women.

METHODS: Population-based cohort study with women aged ≥45 years who filled ≥2 consecutive prescriptions for estrogen-only HT, identified from linked provincial health administrative data from Alberta, Canada, between 2008 and 2019. The primary outcome, incident hypertension, was identified using standardized *International Classification of Diseases, Ninth and Tenth Revision*. Cox proportional hazard models were used to calculate hazard ratios (HRs) for hypertension in women using oral HT compared with nonoral HT (transdermal, vaginal, or intramuscular).

RESULTS: In total, 112 240 women used an estrogen-only form of HT. Oral estrogen was associated with a higher risk of hypertension compared with both transdermal (HR, 1.14 [95% CI, 1.08–1.20]) and vaginal (HR, 1.19 [95% CI, 1.13–1.25]) estrogens. Conjugated equine estrogen was associated with an increased risk of hypertension compared with estradiol (HR, 1.08 [95% CI, 1.04–1.14]) but not estrone (HR, 1.00 [95% CI, 0.93–1.10]). Duration of estrogen exposure and cumulative dose of estrogen was positively associated with risk of hypertension.

CONCLUSIONS: Oral estrogen-only HT use was associated with an increased risk of hypertension in women. In women using estrogen-only HT, nonoral estradiol at the lowest dose and for the shortest time-period is associated with the lowest risk of hypertension.
***(Hypertension.* 2023;80:1463–1473. DOI: 10.1161/HYPERTENSIONAHA.122.19938.)** • **Supplement Material**.

Key Words: estrogens ■ estradiol ■ hypertension ■ menopause ■ pharmacoepidemiology

Hypertension is the leading modifiable risk factor for premature death and both cardiovascular and kidney diseases in women worldwide[1]; this risk increases sharply after menopause.[2] Globally, >1 billion women will be menopausal by the year 2025.[3] Three quarters of women undergoing the menopausal transition experience vasomotor symptoms (VMS) that, on average, persist for 7.4 years.[4] International guidelines[5] suggest that hormone therapy (HT) is the most effective treatment of VMS, such as hot flashes and night sweats. Although use of HT remains the gold standard for relief of VMS and is indicated for short term use,[5] the long-term effects of HT on cardiovascular health outcomes has become increasingly important. Previous data examining the use of combined HT suggested potential cardiovascular harm.[6,7] However, studies examining the effect of oral estrogen alone suggest that nonoral routes of estrogen administration, such as transdermal, may be associated with a lower risk of cardiovascular

Correspondence to: Sofia B. Ahmed, University of Calgary, 3230 Hospital Dr NW, Room 2AC70, Calgary, Alberta, Canada, T2N 4Z6. Email sofia.ahmed@albertahealthservices.ca
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.122.19938.
For Sources of Funding and Disclosures, see page 1472.

Hypertension is available at www.ahajournals.org/journal/hyp

ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

Hypertension is the leading global cause of premature mortality in women and increases sharply with the menopausal transition.

The effect of postmenopausal hormone replacement therapy on blood pressure is uncertain but may be related to route of estrogen administration and formulation of estrogen.

What Is Relevant?

Blood pressure screening and monitoring is important in menopausal individuals, especially after the initiation of estrogen-only menopausal hormone therapy.

Clinical/Pathophysiological Implications?

The results of our prospective study of 112 240 women using an estrogen-only form of hormone therapy suggest that nonoral estradiol at the lowest dose and for the shortest time period is associated with the lowest risk of hypertension.

Nonstandard Abbreviations and Acronyms

CEE	conjugated equine estrogen
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
HT	hormone therapy
ICD	*International Disease Classification*
KEEPS	Kronos Early Estrogen Prevention Study
VMS	vasomotor symptoms
WHI-OS	Women's Health Initiative Observational Study

outcomes.[8–12] Previous studies have reported an increased risk of cardiovascular disease with use of HT, though many have included concomitant estrogen and progestin use and few have controlled for the route of administration, estrogen type, dose, or duration of use.[13] A recent systematic review examining these key factors concluded that the quality of evidence included was generally low or moderate,[10] highlighting a need for more rigorous research to better understand the associations between HT and cardiovascular health in this growing population of females.

The high global prevalence of hypertension in women,[14] coupled with the uncertainty of the effect of postmenopausal estrogen use on blood pressure, led to this examination of the association between estrogen route of administration and incident hypertension in a population-based cohort. In addition, we sought to determine whether estrogen formulation, cumulative dose, and duration of use were associated with risk of incident hypertension.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This prospective cohort study used de-identified, population-based administrative data holdings from the province of Alberta, Canada (population 4.4 million). The University of Calgary Conjoint Health Research Ethics Board approved this study (Ethics ID: REB20-0093). This analysis is reported according to the Reporting of studies Conducted using Observational Routinely collected Data guidelines.

Data Sources

Data sources include the Physician Claims Database, National Ambulatory Care Classification Database, Discharge Abstract Database, and data on dispensed prescription medication from the Pharmaceutical Information Network, which collects information from all outpatient pharmacies in the province of Alberta. These databases were originally created for health care management and monitoring (eg, insurance claims and remunerating physicians) under the universal health care system in Canada. The databases are suitable for research purposes as they contain rich information at the population level and have mechanisms to ensure high data quality. These data holdings in Alberta are maintained by Alberta Health and Alberta Health Services and cover >99.0% of the general population of the province. Deterministic linkage using the personal health number, sex, and date of birth were used to link records from multiple data sets.

Identification of Study Cohort

Women aged ≥45 years who filled ≥2 prescriptions for the same form of postmenopausal HT for a minimum of 6 months between April 1, 2008 and March 31, 2019, were included in the cohort. The prevalence of transgender individuals is 0.5% to 1.6%.[15] We assumed that any participants who filled prescriptions for estrogen identified as women. Incident HT prescriptions were determined by applying a 1-year washout period before the first recorded filled prescription. Eligible HT prescriptions were identified using the Anatomic Therapeutic Chemical Chemical Classification System,[16] an international coding schema related to a specific drug or class of drugs developed by the World Health Organization (see Supplemental Material for list of relevant Anatomical Therapeutic Chemical

codes). Corresponding Drug Identification Numbers were used to identify the HT formulation, including dosage and route of administration.

Women were deemed nonadherent to postmenopausal HT if there was a gap of >6 months between dispensed dates and were excluded from analysis. Women who filled a prescription for one formulation of HT and then filled a prescription for another formulation of HT during the study period were classified as having switched treatment and were also excluded from the analysis.

Measures of Exposure

Use of HT was identified through multiple approaches. The first approach categorized HT exposure using 3 mutually exclusive groups: (1) estrogen-only use: at least 6 months of use and no prescriptions for progestin; (2) progestin-only use: at least 6 months of use and no prescriptions for estrogen; (3) estrogen and progestin combined use: at least 6 months of prescriptions for estrogen and 6 months prescription for progestin. To investigate the effects of estrogen alone on the primary outcome, only women who filled prescriptions for estrogen-only HT were included in this analysis. Estrogen exposure was categorized by the route of administration ([1] oral; [2] transvaginal; [3] transdermal; and [4] intramuscular) and by formulation of estrogen. Cumulative estrogen dose was calculated using the defined daily dose provided by the World Health Organization and multiplying by the exposure period. Duration of estrogen use was determined by calculating the time between the first and last prescription dispensed dates or the end of the study period.

Definition of Outcomes

The primary outcome of incident hypertension was defined using the following validated criteria: (1) 2 or more physician claims for hypertension within 2 years; or (2) one recording of hypertension in the hospital discharge abstract with a primary or secondary diagnosis of hypertension.[17] We identified hypertension cases using the *International Disease Classification* (*ICD*) codes (*ICD*-9-CM: 401.x, 402.x, 403.x, 404.x, 405.x; *ICD*-10-CA: I10.x, I11.x, I12.x, I13.x, I15.x). Cases were deemed incident if the hypertension diagnosis occurred after the HT prescription start date. The sensitivity of this case definition for hypertension is 66% to 72% with a specificity of 95% to 97%, positive predictive value of 77% to 87%, and negative predictive value of 88% to 5%.[17,18]

Measuring Covariates

A measurement of comorbidity status, based on *ICD*-9 and *ICD*-10 codes, was calculated using the Elixhauser comorbidity index.[19]The Elixhauser comorbidity index is a method of categorizing comorbidities of patients based on the *ICD* diagnosis codes found in administrative data. Each comorbidity category is dichotomous; it is either present or it is not to produce an overall score for the Elixhauser Index. The original Elixhauser comorbidity index includes 30 disease conditions, however, hypertension was removed as a comorbidity as it was the primary outcome of the study.

Statistical Analysis

Baseline characteristics by route of estrogen administration were presented as the mean ± SD for normally distributed continuous variables and number (percentages) for categorical variables. Differences in baseline characteristics across categories of estrogen routes of administration were determined using independent *t* tests and Kruskal-Wallis tests, where appropriate. Cox proportional hazard models were used to calculate hazard ratios (HR) for the risk of hypertension in women using oral estrogen compared with nonoral routes of estrogen therapy (transdermal, vaginal, or intramuscular). The HR for the route of estrogen administration and risk of hypertension were controlled for age, rural status, Elixhauser comorbidity score, duration of exposure in years, daily defined dose, estrogen formulation, and the interaction variable of route of administration and estrogen formulation. The HR of the estrogen formulation and risk of hypertension were controlled for age, rural status, Elixhauser comorbidity score, duration of exposure in years, daily defined dose, route of administration. The interaction between the variable route of administration and formulation of estrogen was tested, and if significant was included in the model. Furthermore, the interaction between age and duration of use was tested and if significant was included in the model. Models were stratified by 10-year age cohort (based on age of initiation) and interaction terms were tested to assess for potential multiplicative effects of age cohort, route of estrogen administration and formulation of estrogen. Margins plots were employed to illustrate the predictive probability of hypertension with increasing cumulative dose or duration of use. Sensitivity analyses were conducted restricting the study population to women who had ≤4 months between estrogen prescription dispensed dates for a more conservative definition of continuous use based upon common prescribing practices.

RESULTS

Baseline Characteristics

Of the 229 636 participants who filled at least 2 prescriptions for estrogen HT between 2008 and 2019, 112 240 participants were classified as estrogen-only users (Figure 1). Baseline participant characteristics by route of administration of estrogen use are shown in Table 1. The most common route of estrogen use was vaginal, followed by oral and transdermal use. There were 15 participants using only intramuscular estrogen, and they were excluded from further analysis due to low numbers. The most common age of initiation of estrogen use was between 50 and 59 years and women who used transdermal HT were significantly younger than both oral (P=0.02) and vaginal (P=0.03) HT users. Upon stratification by estrogen route of administration, 3 quarters of women used a nonoral estrogen (Table 1). Of the estrogen-only hormone therapies dispensed, 3 formulations of synthetic estrogen were present, with the majority being estradiol (55%) and conjugated equine estrogen (CEE; 40%), and a small minority using estrone (5%). Oral estrogen use was mainly CEE, while transdermal and vaginal HT use was primarily estradiol. The majority of women exceeded 3 years of estrogen use (median, 4.7 years [interquartile range, 2.4–7.4]), irrespective of route of administration. The percentage of participants

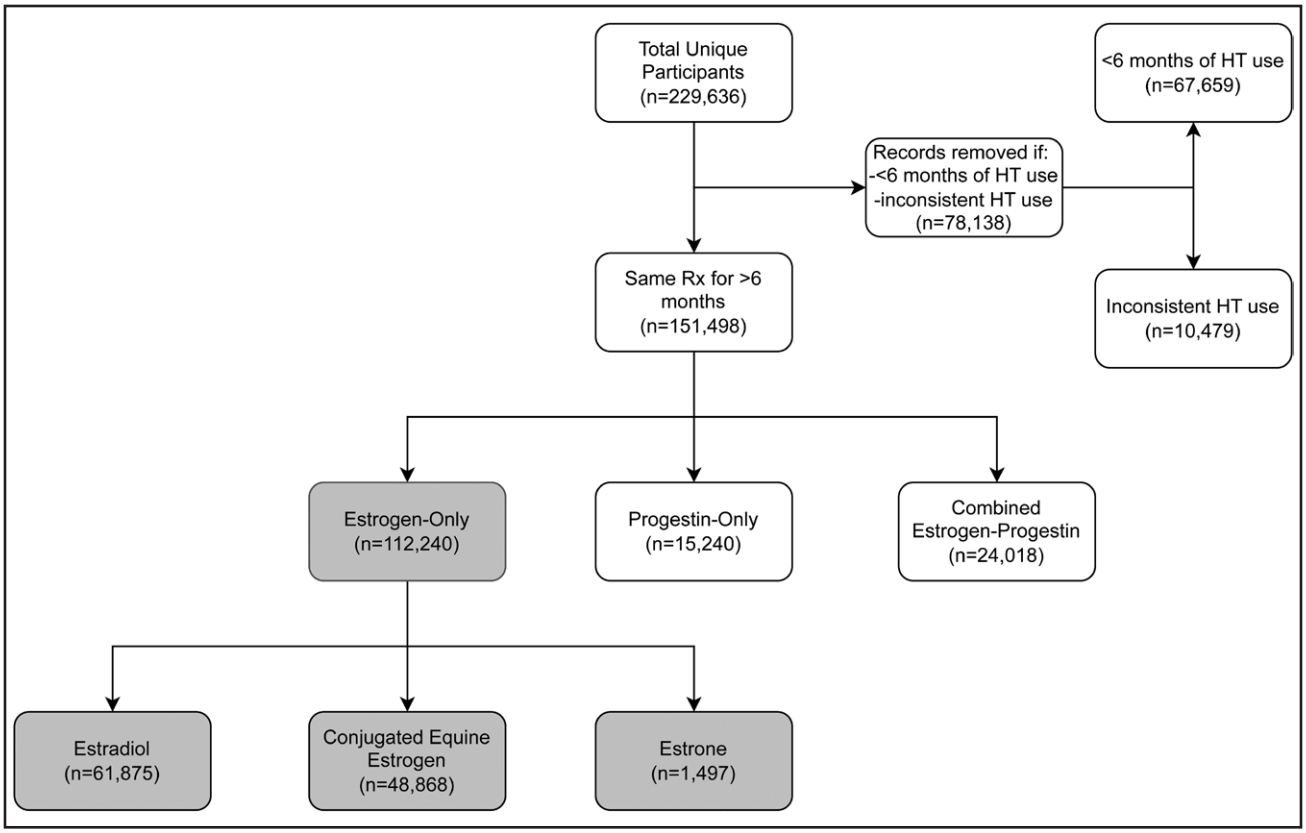

Figure 1. Study flow diagram.
HT indicates hormone therapy hormone therapy.

with a rural status did not differ by route of administration (P=0.75). Oral estrogen users had a significantly higher comorbidity score compared with transdermal or vaginal estrogen users (P=0.001).

Route of Estrogen Administration and Risk of Hypertension

Oral estrogen, as compared with both transdermal and vaginal, was associated with an increase in incident hypertension (oral versus transdermal: HR, 1.14 [95% CI, 1.08–1.20]; oral versus vaginal: HR, 1.19 [95% CI, 1.13–1.25]). Age cohorts significantly modified the association between the route of estrogen administration and the risk of hypertension (Figure 2). Stronger associations were observed with oral compared with transdermal estrogen use and hypertension younger compared with older age cohorts (P<0.02 for trend), while stronger associations were observed between oral and vaginal estrogen use and hypertension in older compared with younger age cohorts (P<0.001 for trend). No differences in the risk of hypertension were observed between transdermal and vaginal estrogen uses across age cohorts (Figure S1). There was a multiplicative effect between route of administration and formulation of estrogen (P=0.023), and this interaction term was included in the analyses.

Formulation of Estrogen and Risk of Hypertension

Use of CEE was associated with an increased risk of hypertension when compared with estradiol (CEE versus estradiol, 1.08 [95% CI, 1.04–1.14]) but not estrone (CEE versus estrone, 1.00 [95% CI, 0.93–1.10]; Figure 3). Age cohort significantly modified the association between CEE and risk of hypertension (P<0.001). No differences in risk of incident hypertension were observed with estradiol compared with estrone use (Figure S2). There was a multiplicative effect between route of administration and formulation of estrogen (P=0.023), and this interaction term was included in the analyses.

Duration of Estrogen Exposure and Risk of Hypertension

Duration of estrogen exposure was positively and significantly associated with risk of hypertension (Figure 4A and 4B). When stratified by route of administration, longer duration of oral estrogen use was significantly associated with the greatest increase in the risk of hypertension, followed by vaginal and transdermal use (Figure 4A). When stratified by estrogen formulation, the strongest associations with risk of hypertension were observed with longer duration of CEE and estrone use,

Table 1. Descriptive Characteristics

Characteristics	Oral (n=26 671)	Nonoral (n=85 569)	
		Vaginal (n=70 576)	Transdermal (n=14 993)
Age, y	58 (10)	62 (10)*	55 (8)*†
Estrogen type			
Estradiol	3332 (12%)	43 562 (62%)	14 993 (100%)
Conjugated equine estrogen	22 286 (84%)	26 570 (24%)	0
Estrone	1053 (4%)	444 (<1%)	0
Age of initiation, y			
<50	5677 (21%)	5450 (8%)	4049 (27%)
50–59	10 757 (40%)	29 137 (42%)	7296 (49%)
60–69	6287 (24%)	20 108 (28%)	2653 (18%)
70–79	2931 (11%)	10 388 (15%)	824 (5%)
>80	1019 (4%)	5493 (7%)	171 (1%)
Duration of use, y			
<1	1863 (7%)	8158 (12%)	1108 (7%)
1–3	5681 (21%)	20 884 (30%)	3269 (22%)
3–6	6270 (24%)	19 962 (28%)	3710 (25%)
≥6	12 857 (48%)	21 572 (30%)	6906 (46%)
Rural status	3252 (12%)	11 7763 (11%)	1799 (12%)
Elixhauser comorbidity score	1.33 (0.7)	1.20 (0.70)*	1.18 (0.6)*†

Baseline characteristics by route of estrogen administration were presented as the mean±SD for normally distributed continuous variables and number (percentages) for categorial variables. Differences in baseline characteristics across categories of estrogen routes of administration were determined using independent *t* tests and Kruskal-Wallis tests, where appropriate.

*Data representing statistical significant values ($P<0.05$) compared with use of oral estrogen therapy.

†Data representing statistical significant values ($P<0.05$) compared with use of vaginal estrogen therapy.

with a weaker association observed with duration of estradiol use (Figure 4B).

Cumulative Estrogen Dose and Risk of Hypertension

Higher daily doses of estrogen, independent of the route of administration or type of estrogen, were significantly associated with a linear increase in the probability of hypertension (Figure 4C and 4D). Higher daily estrogen dose in oral form, compared with the same dose in transdermal and vaginal form, was associated with a significantly greater risk of hypertension (Figure 4C). Analysis of daily dose by estrogen formulation demonstrated that estradiol use was associated with the lowest risk of hypertension compared with the same estrogen dose with CEE and estrone (Figure 4D).

Sensitivity Analysis

Restricting the study population to participants who had ≤4 months between estrogen prescription dispensed dates did not significantly alter the results (data not shown).

DISCUSSION

To date, this is the largest study examining the associations between route of administration, formulation, duration of use and cumulative dose of estrogen and the risk of hypertension in postmenopausal women. The key findings of this study are as follows: (1) oral, compared with both transdermal and vaginal, estrogen use was associated with an increased risk of hypertension; (2) estradiol, compared with CEE, was associated with a reduced risk of hypertension; (3) there was a dose-response relationship between cumulative estrogen exposure and risk of hypertension; (4) longer duration of estrogen exposure was associated with increased risk of hypertension. Taken together, these data suggests that in women using estrogen-only HT, use of nonoral estradiol at the lowest dose and for the shortest period of time may minimize the risk of incident hypertension.

In women who are experiencing VMS or premature menopause, HT is recommended.[5,7] Although multiple studies have examined the effect of HT on cardiovascular outcomes,[20–24] few studies have specifically examined route of estrogen administration. The KEEPS (Kronos Early Estrogen Prevention Study) randomized 727 healthy postmenopausal women within 3 years of their final menstrual period to either oral CEE 0.45 mg/d, transdermal estradiol patch 50 µg/d or placebo.[23] After 4 years of follow-up, oral CEE use was associated with greater increases in HDL-C (high-density lipoprotein cholesterol), triglycerides and hs-CRP (high sensitivity C-reactive protein) than use of transdermal estradiol or

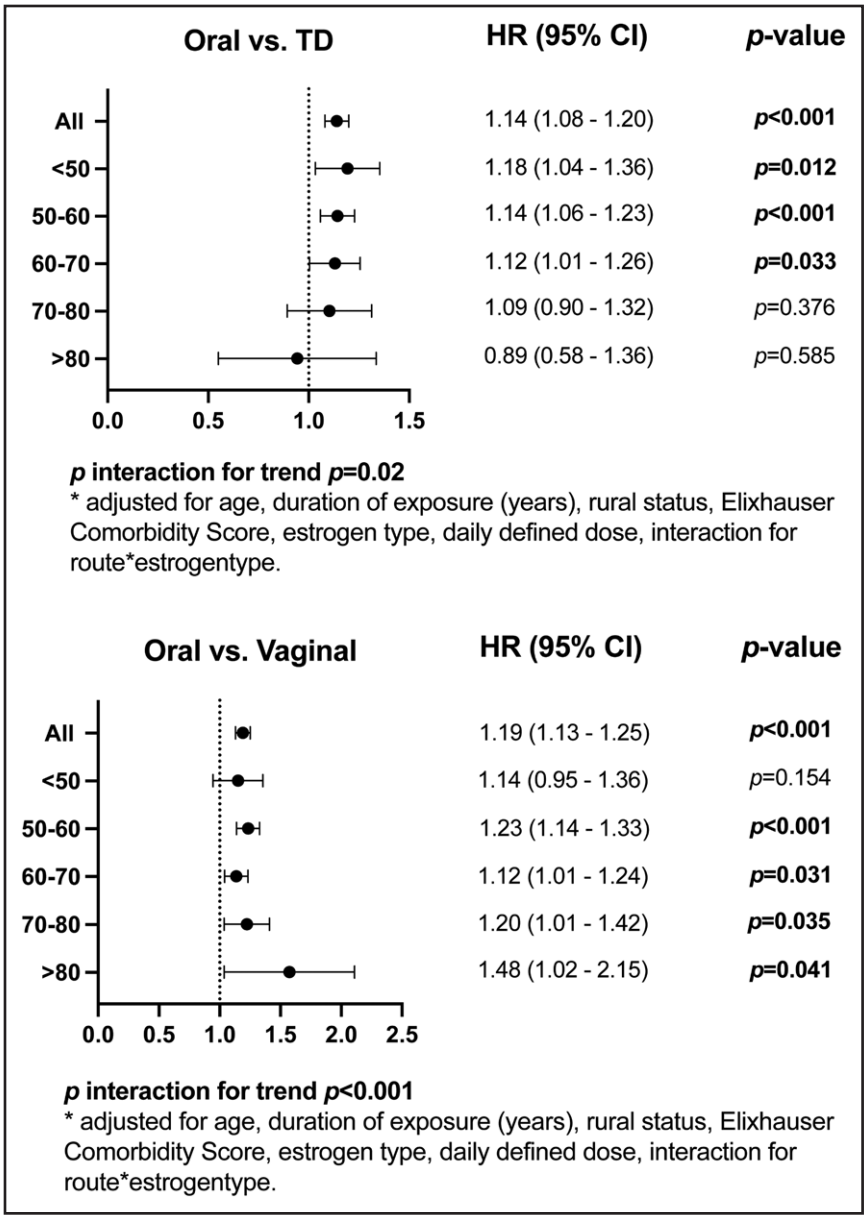

Figure 2. Hazard ratios (HR) for the risk for hypertension by route of administration of hormone therapy, stratified by 10-year age cohort.

placebo.[23] This study did not observe differences in progression of atherosclerosis using carotid intima-media thickness by estrogen formulation, which may be because participants were free of subclinical coronary atherosclerosis at trial entry, younger (53 years old) and tended to have low baseline body mass index, blood pressure and lipid values, thus potentially impacting the study's generalizability.[23] The WHI-OS (Women's Health Initiative Observational Study) evaluated the association between HT dose, formulation, route of administration, and risk of cardiovascular events in 93 676 postmenopausal women over a 10.4 year follow-up period. Similar to our findings, the transdermal route of administration, lower dose estrogen, and estradiol (as compared with CEE) were associated with lower risks of cardiovascular disease.[8] A smaller WHI-OS study of normotensive participants using menopausal HT (n=19 986) demonstrated that compared with CEE with or without a progestin, the odds for newly treated hypertension were lower in women who used transdermal estradiol or oral estrone sulphate dominant preparations.[12] Of note, participants in the WHI-OS were a highly select population group with concomitant progestin use while participants in our study were an unselected community-based cohort using estrogen-only therapy which may account for differences in study outcomes. A French prospective population-based study of normotensive women using menopausal HT reported that oral but not transdermal estrogen use was associated with an increased risk of hypertension, particularly in combination with a progestogen such as pregnane and norpregnane derivatives.[11] An important distinction to note in our study is the exclusion of women using combination menopausal HT to avoid any potential influence of progestins on the risk of hypertension.

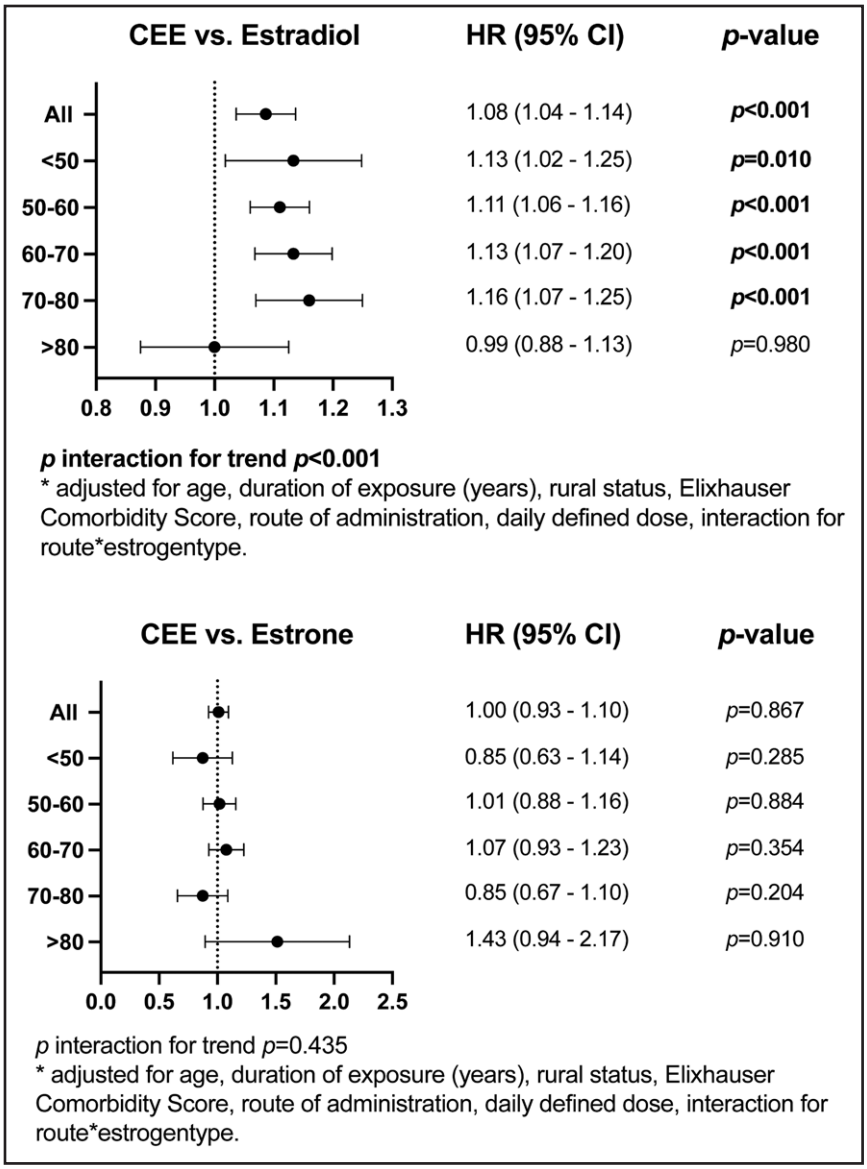

Figure 3. Hazard ratios (HR) for the risk for hypertension by type of estrogen, stratified by 10-year age cohort.
CEE indicates conjugated equine estrogen.

Previous studies in normotensive postmenopausal women have demonstrated reductions in blood pressure with transdermal, but not oral estrogen use.[12,25–27] Differences in pharmacokinetics may explain the distinctions in hypertension risk observed by route of estrogen administration. Oral estrogen, unlike nonoral formulations, undergoes first-pass hepatic metabolism which has been hypothesized to result in activation of the renin angiotensin aldosterone system.[8,25,28] In the liver, hepatic angiotensinogen mRNA production is responsive to estrogen, leading to greater downstream angiotensin II levels.[29] Angiotensin II is a powerful vasoconstrictor associated with significant increases in blood pressure.[30] Transvaginal delivery of estrogen concentrates hormone locally and provides a low systemic hormonal exposure.[31] Thus, increased renin angiotensin aldosterone system activation provides a potential biological explanation for the greater risk of hypertension associated with oral estrogen exposure, though this was not examined in our study so remains a theoretical underlying explanation.

Previous studies have not directly compared formulation of exogenous estrogen while also controlling for route of administration. In a study of 222 of postmenopausal women randomized to either oral estradiol or placebo, there was no change in blood pressure after 2 years.[32] In contrast, oral CEE (n=5994) has been associated with increased risk of hypertension compared with placebo (n=5679) after 5.6 years.[33]To our knowledge, there are no studies that investigate the effect of exogenous estrone on cardiovascular disease.

Animal studies have suggested a dose-response association between estrogen and measures of cardiovascular risk, with higher doses of estrogen in ovariectomized mice resulting in increased cardiac and kidney injury and death.[34] Large observational studies in postmenopausal women[8,35] reported that lower doses of CEE (0.3 mg/d) were associated with a nonsignificant trend towards a

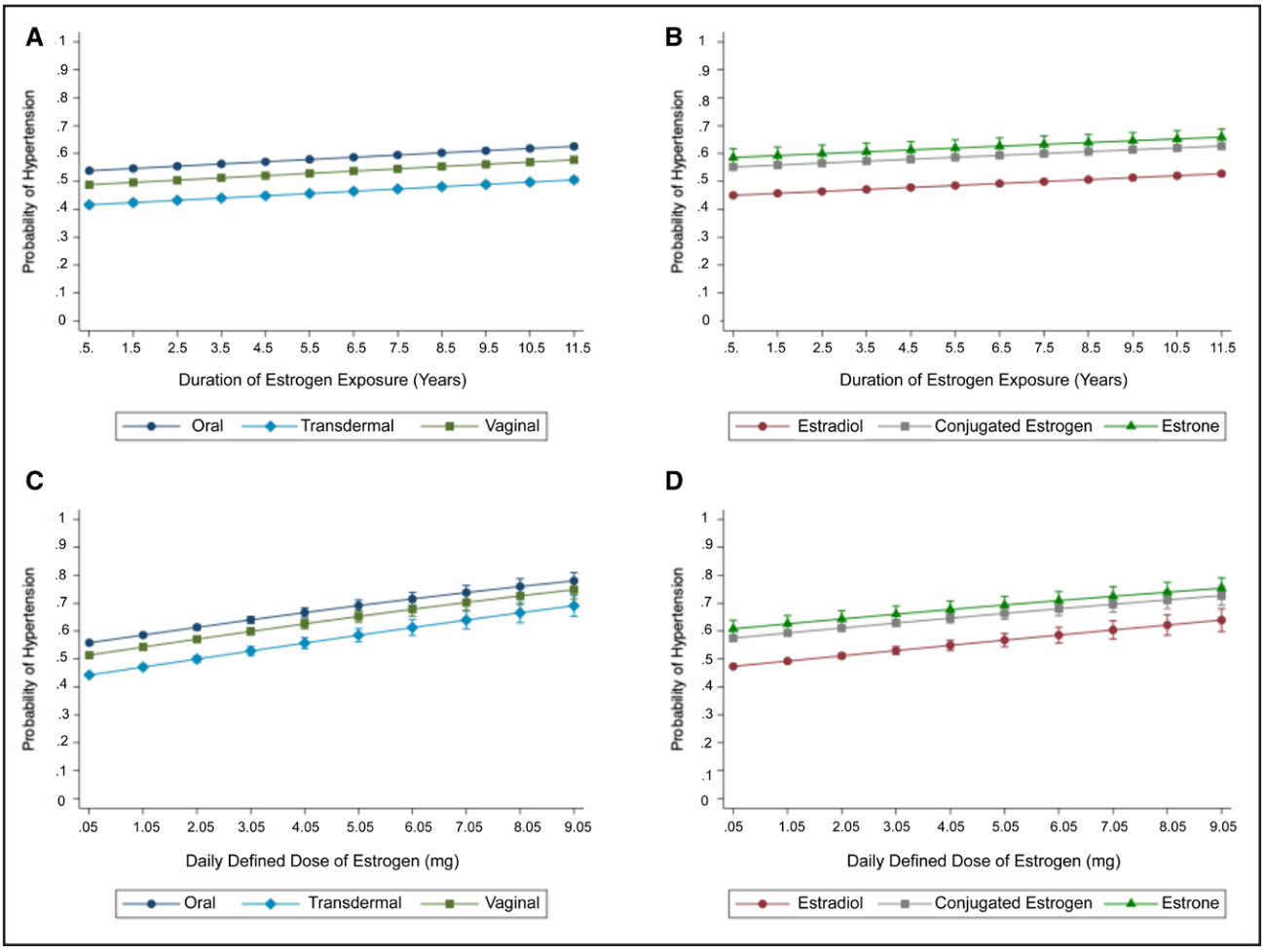

Figure 4. Probability of hypertension as function of duration of estrogen exposure and daily defined dose of estrogen.
A and **B**, Duration of estrogen exposure. **C** and **D**, Daily defined dose of estrogen. Data was stratified by route of administration and estrogen formulation.

decreased risk of cardiovascular events compared with standard dose (0.625 mg). In addition, the standard dose was associated with an increased risk of stroke.

For women 10 or more years past menopause at time of menopausal HT, incident self-reported treated hypertension was significantly greater with higher dose CEE compared with 0.625 mg CEE.[12] Of note, there is very low systemic bioavailability (2%–10%) with oral estrogen due to gut and liver absorption, therefore, higher doses are required to be effective,[28] which may compound any risk associated with oral forms of estrogen.

Our finding that the association between oral estrogen use and risk of hypertension was greatest in younger women deserves particular emphasis. A reanalysis of the Women's Health Study suggested that women who initiated combined HT (eg, oral CEE and medroxyprogesterone) before 60 years of age and within 10 years of menopause benefitted from a cardiovascular perspective;[6] this is often referred to as the timing hypothesis. Similar findings have been observed in a review of Nurses' Health Study publications,[36] where younger women who are closer to menopause onset have a more favorable risk-benefit profile than do older women from use of HT for relief of VMS. Although we were not able to confirm at what age participants achieved menopause, the average age of natural menopause in Canada is 51 years.[37] Considering these findings, our study suggested that in young women, although HT may be beneficial closer to menopausal onset, the route of administration may play a great role in mediating the risk for hypertension, with oral forms demonstrating a greater harm. Alternatively, in older cohorts (70–80 and >80 years) the route of administration and estrogen type has a looser association with the risk of hypertension. It is important to note that our study did not include a nonestrogen user control group and so we are unable to examine the risk of hypertension with estrogen use in our study compared with those not using any formulation of HT, but only on the risk of hypertension with oral compared with transdermal and transvaginal estrogen use. However, the objective of this study was to compare different routes and formulations of estrogen therapy among individuals taking HT on

the risk of hypertension. Women not taking HT are not comparable to those taking estrogen as presumably they lack an indication for this medication.

This study has limitations. We were restricted in our assessment of clinical data due to use of administrative data. Specifically, although we could not confirm the postmenopausal state, the most common indication of estrogen therapy initiation in this age group is for the management of menopausal symptoms,[5] and therefore, it is unlikely that the study participants were not menopausal. Oral and transdermal estrogen are used for VMS; while vaginal estrogen can also be used for this indication,[38,39] it is frequently used for genitourinary symptoms. However, both transdermal and vaginal estrogen avoid the first-pass metabolism required by use of oral estrogen, suggesting that nonoral use of estrogen, irrespective of indication, may be a safer option in those at risk of hypertension. Our primary outcome of hypertension was ascertained using administrative data, which relies on physician billing claims and is thus prone to underreporting.[18] Previous algorithms have missed up to 28% of cases of hypertension when compared with audits of primary care physicians[18]; however, while our results may underestimate the true incidence of hypertension in this population over the study period, this under-ascertainment is unlikely to differ by estrogen use. Furthermore, there are racial/ethnic disparities in hypertension prevalence, awareness, treatment, and control[40]; however, due to the nature of the administrative data used in this study, we were not able to describe the race/ethnicity composition of the cohort. Next, oral estrogen has been associated with rapid loss of kidney function.[41] Although kidney disease and hypertension are closely interconnected pathophysiologic states, we used the Elixhauser comorbidity index to control for comorbidities, including kidney disease. The World Health Organization's defined daily dose is the assumed average maintenance dose for a drug used for its main indication in adults. The clinically prescribed estrogen dose for oral estradiol, CEE, transdermal estrogen, and vaginal estradiol are very different, and a direct comparison of the same defined daily dose of estrogen by route of administration may not be appropriate. However, our study demonstrates that independent of route of administration, there was a dose dependent effect of estrogen dose on the risk of hypertension. The study population was limited to users of estrogen-only menopausal HT, and the results may thus not be applicable to women who use combined estrogen and progestin HT. However, by restricting our study population to estrogen-only users, it allowed us to investigate the independent associations of route of administration, formulation, duration of use and dose of estrogen on hypertension while minimizing confounding factors. Furthermore, we do not have hysterectomy data on the participants, however, oral and transdermal estrogen-only users (n=41 664) represented 27% of the total population using any form of menopausal HT (n=151 526), which is consistent with the population who have undergone hysterectomy in Alberta.[42] The prevalence of self-reported hysterectomies in Alberta stratified by age cohort is as follows: 50 to 59 years, 24% and 60 to 69, 39.4%.[42] Finally, we were unable to control for known hypertension risk factors, such as obesity, and smoking status. In observational studies, women who take nonoral forms of HT are generally better educated, have higher incomes and better access to health care,[43] and are healthier even before starting therapy; these factors may have also played a role in women who were excluded from the study because they used HT for <6 months or inconsistently. However, restricting our analyses to a shorter duration of continuous use did not significantly alter our findings, and the results from this study are in keeping with prospective cohort studies which did control for these important factors. Furthermore, we were able to control for exposure to HT in the prestudy period as well as duration of therapy.

This study also has many strengths. The size of this population-based cohort with over 10 years of follow up increases the generalizability of our findings. As far as we are aware, this is the first study to evaluate the specific effects of route of administration, formulation, duration of use and dose of estrogen on the risk of hypertension. Additionally, the use of computerized drug prescription data eliminates the impact of recall bias of study participants.

PERSPECTIVES

In this community-based population, oral, as compared with vaginal or transdermal, estrogen use was associated in a dose-dependent manner with an increased risk of incident hypertension, particularly in women closer to the menopausal transition period. Longer duration of estrogen use was associated with a greater risk of incident hypertension, and use of estradiol as compared with other forms of estrogen was associated with a lower risk of hypertension. Taken together, our results suggest that blood pressure should be monitored closely in women using estrogen-only HT. Although menopause is a normal part of the female aging process, it can often be a prolonged disruptive period that causes symptoms for the majority of women and knowledge of effective and safe hormonal treatments remains limited.[44] Large, prospective, randomized studies that take into account the complexities of estrogen therapy, including route of administration, formulation, dose, duration of use, timing of imitation and concomitant progestin use are required before proposing changes to clinical practice.

ARTICLE INFORMATION

Received June 29, 2022; accepted March 21, 2023.

ORIGINAL ARTICLE

Affiliations

Cumming School of Medicine (C.Z.K., A.M., M.R., K.A.N., J.M.M., S.B.A.), Libin Cardiovascular Institute of Alberta (C.Z.K., A.M., K.A.N., J.M.M., S.B.A.), and O'Brien Institute for Public Health (A.M., K.A.N.), University of Calgary, Alberta, Canada. Alberta Kidney Disease Network, Calgary, Alberta, Canada (J.M.M., S.B.A.). Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada (A.M.).

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345:1291–1297. doi: 10.1056/nejmoa003417
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603. doi: 10.1161/CIR.0000000000000485
3. Allen C, Evans G, Sutton EL. Pharmacologic therapies in women's health: contraception and menopause treatment. *Medical Clinics*. 2016;100:763–789. doi: 10.1016/j.mcna.2016.03.008
4. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, Hess R, Joffe H, Kravitz HM, Tepper PG, et al; Study of Women's Health Across the Nation. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA internal medicine*. 2015;175:531–539. doi: 10.1001/jamainternmed.2014.8063
5. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2018;25:1362–1387. doi: 10.1097/GME.0000000000001241
6. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson G, Howard BV, Thomson CA, LaCroix AZ, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310:1353–1368. doi: 10.1001/jama.2013.278040
7. De Villiers T, Hall J, Pinkerton J, Pérez SC, Rees M, Yang C, Pierroz DD. Revised global consensus statement on menopausal hormone therapy. *Maturitas*. 2016;91:153–155. doi: 10.1016/j.maturitas.2016.06.001
8. Shufelt CL, Merz CNB, Prentice RL, Pettinger MB, Rossouw JE, Aroda VR, Kaunitz AM, Lakshminarayan K, Martin LW, Phillips LS, et al. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the WHI observational study. *Menopause*. 2014;21:260–266. doi: 10.1097/GME.0b013e31829a64f9
9. Bezwada P, Shaikh A, Misra D. The effect of transdermal estrogen patch use on cardiovascular outcomes: a systematic review. *J Womens Health (Larchmt)*. 2017;26:1319–1325. doi: 10.1089/jwh.2016.6151
10. Oliver-Williams C, Glisic M, Shahzad S, Brown E, Pellegrino Baena C, Chadni M, Chowdhury R, Franco OH, Muka T. The route of administration, timing, duration and dose of postmenopausal hormone therapy and cardiovascular outcomes in women: a systematic review. *Hum Reprod Update*. 2019;25:257–271. doi: 10.1093/humupd/dmy039
11. Madika AL, MacDonald CJ, Fournier A, Mounier-Vehier C, Beraud G, Boutron-Ruault MC. Menopausal hormone therapy and risk of incident hypertension: role of the route of estrogen administration and progestogens in the E3N cohort. *Menopause*. 2021;28:1204–1208. doi: 10.1097/GME.0000000000001839
12. Wild RA, Larson JC, Crandall CJ, Shadyab AH, Allison M, Gass M, Shufelt C, Manson JE. Hormone therapy formulation, dose, route of delivery, and risk of hypertension: findings from the Women's Health Initiative Observational Study (WHI-OS). *Menopause*. 2021;28:1108–1116. doi: 10.1097/GME.0000000000001828
13. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med*. 2003;348:645–650. doi: 10.1056/NEJMsb022365
14. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16:223–237. doi: 10.1038/s41581-019-0244-2
15. Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. *Lancet*. 2016;388:390–400. doi: 10.1016/S0140-6736(16)00683-8
16. World Health Organization Collaborating Center for Drug Statitics Methodology. ATC/DDD Index 2022. 2022. https://www.whocc.no/atc_ddd_index/
17. Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, Hill MD, Ghali WA, McAlister FA; Hypertension Outcome and Surveillance Team of the Canadian Hypertension Education Programs. Validation of a case definition to define hypertension using administrative data. *Hypertension*. 2009;54:1423–1428. doi: 10.1161/HYPERTENSIONAHA.109.139279
18. Tu K, Campbell NR, Chen Z-L, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open medicine*. 2007;1:e18.
19. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36:8–27. doi: 10.1097/00005650-199801000-00004
20. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SAA, Howard BV, Johnson KC, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333. doi: 10.1001/jama.288.3.321
21. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SAA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701–1712. doi: 10.1001/jama.291.14.1701
22. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, Selzer RH, Liu Cr CR, Liu Ch CH, Azen SP; Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001;135:939–953. doi: 10.7326/0003-4819-135-11-200112040-00005
23. Miller VM, Naftolin F, Asthana S, Black DM, Brinton EA, Budoff MJ, Cedars MI, Dowling NM, Gleason CE, Hodis HN, et al. The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned? *Menopause*. 2019;26:1071–1084. doi: 10.1097/GME.0000000000001326
24. Chiu CL, Lujic S, Thornton C, O'Loughlin A, Makris A, Hennessy A, Lind JM. Menopausal hormone therapy is associated with having high blood pressure in postmenopausal women: observational cohort study. *PLoS One*. 2012;7:e40260. doi: 10.1371/journal.pone.0040260
25. Ichikawa J, Sumino H, Ichikawa S, Ozaki M. Different effects of transdermal and oral hormone replacement therapy on the renin-angiotensin system, plasma bradykinin level, and blood pressure of normotensive postmenopausal women. *Am J Hypertens*. 2006;19:744–749. doi: 10.1016/j.amjhyper.2005.10.006
26. Akkad AA, Halligan AW, Abrams K, Al-Azzawi F. Differing responses in blood pressure over 24 hours in normotensive women receiving oral or transdermal estrogen replacement therapy. *Obstet Gynecol*. 1997;89:97–103. doi: 10.1016/s0029-7844(97)84258-5
27. Vongpatanasin W, Tuncel M, Mansour Y, Arbique D, Victor RG. Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation*. 2001;103:2903–2908. doi: 10.1161/01.cir.103.24.2903
28. O'Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol*. 1995;35:18S–24S. doi: 10.1002/j.1552-4604.1995.tb04143.x
29. Deschepper CF. Angiotensinogen: hormonal regulation and relative importance in the generation of angiotensin II. *Kidney Int*. 1994;46:1561–1563. doi: 10.1038/ki.1994.446
30. Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH, Danser AJ. Hypertension: renin–angiotensin–aldosterone system alterations. *Circ Res*. 2015;116:960–975. doi: 10.1161/circresaha.116.303587
31. Cicinelli E. Intravaginal oestrogen and progestin administration: advantages and disadvantages. *Best Pract Res Clin Obstet Gynaecol*. 2008;22:391–405. doi: 10.1016/j.bpobgyn.2007.08.010
32. Steiner AZ, Hodis HN, Lobo RA, Shoupe D, Xiang M, Mack WJ. Postmenopausal oral estrogen therapy and blood pressure in normotensive and hypertensive subjects: the Estrogen in the Prevention of Atherosclerosis Trial. *Menopause*. 2005;12:728–733. doi: 10.1097/01.gme.0000184426.81190.01
33. Swica Y, Warren MP, Manson JE, Aragaki AK, Bassuk SS, Shimbo D, Kaunitz A, Rossouw J, Stefanick ML, Womack CR. Effects of oral conjugated equine estrogens with or without medroxyprogesterone acetate on incident hypertension in the Women's Health Initiative hormone therapy trials. *Menopause*. 2018;25:753–761. doi: 10.1097/GME.0000000000001067
34. Meng X, Dai X, Liao T-D, D'Ambrosio M, Wang F, Yang JJ, Yang X-P. Dose-dependent toxic effects of high-dose estrogen on renal and cardiac injury in surgically postmenopausal mice. *Life Sci*. 2011;88:178–186. doi: 10.1016/j.lfs.2010.11.008

35. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;133:933–941. doi: 10.7326/0003-4819-133-12-200012190-00008
36. Bhupathiraju SN, Grodstein F, Stampfer MJ, Willett WC, Hu FB, Manson JE. Exogenous hormone use: oral contraceptives, postmenopausal hormone therapy, and health outcomes in the Nurses' Health Study. *Am J Public Health*. 2016;106:1631–1637. doi: 10.2105/AJPH.2016.303349
37. Costanian C, McCague H, Tamim H. Age at natural menopause and its associated factors in Canada: cross-sectional analyses from the Canadian Longitudinal Study on Aging. *Menopause*. 2018;25:265–272. doi: 10.1097/GME.0000000000000990
38. Speroff L. Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms. *Obstet Gynecol*. 2003;102:823–834. doi: 10.1016/s0029-7844(03)00764-6
39. Krause M, Wheeler TL 2nd, Richter HE, Snyder TE. Systemic effects of vaginally administered estrogen therapy: a review. *Female Pelvic Med Reconstr Surg*. 2010;16:188–195. doi: 10.1097/SPV.0b013e3181d7e86e
40. Aggarwal R, Chiu N, Wadhera RK, Moran AE, Raber I, Shen C, Yeh RW, Kazi DS. Racial/ethnic disparities in hypertension prevalence, awareness, treatment, and control in the United States, 2013 to 2018. *Hypertension*. 2021;78:1719–1726. doi: 10.1161/HYPERTENSIONAHA.121.17570
41. Ahmed SB, Culleton BF, Tonelli M, Klarenbach SW, Macrae JM, Zhang J, Hemmelgarn BR; Alberta Kidney Disease Network. Oral estrogen therapy in postmenopausal women is associated with loss of kidney function. *Kidney Int*. 2008;74:370–376. doi: 10.1038/ki.2008.205
42. Stankiewicz A, Pogany L, Popadiuk C. Prevalence of self-reported hysterectomy among Canadian women, 2000/2001. *Chronic Dis Inj Can*. 2014;34:30–35. doi: 10.24095/hpcdp.34.1.05
43. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am J Epidemiol*. 1996;143:971–978. doi: 10.1093/oxfordjournals.aje.a008678
44. Langer RD, Hodis HN, Lobo RA, Allison MA. Hormone replacement therapy - where are we now? *Climacteric*. 2021;24:3–10. doi: 10.1080/13697137.2020.1851183