Menopause: The Journal of The North American Menopause Society
Vol. 21, No. 7, pp. 769-783
DOI: 10.1097/gme.0000000000000169

PERSONAL PERSPECTIVE

What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead?

James A. Simon, MD, CCD, NCMP, IF, FACOG

Abstract

The author considers hypothetical comparisons between oral conjugated equine estrogens and transdermal estradiol and between oral medroxyprogesterone acetate and oral micronized progesterone for their effects on four primary outcomes of the Women's Health Initiative (WHI): cardiovascular disease risk, cerebrovascular disease risk, venous thromboembolism risk, and breast cancer risk. Although the discussion in this article focuses on transdermal estradiol delivered through patches, gels, or lotions, it could be broadened to include all forms of nonoral estrogen administration. After a brief review of the WHI and a survey of the relevant literature in which the safety of these various hormone therapies is assessed or compared, the author uses statistical methods to ascertain the attributable risk of venous thromboembolism for transdermal estradiol versus oral hormone therapy and imputes those risks into the WHI primary outcomes.

Key Words: Women's Health Initiative – Menopause – Hormone therapy – Transdermal estradiol – Micronized progesterone – Venous thromboembolism.

After the results of the estrogen-progestogen arm of the Women's Health Initiative (WHI) were published in 2002,[1] followed by those of the estrogen-only arm in 2004,[2] many "what-if"-type questions were posed:

- What if the researchers had focused only on women aged 50 to 59 years, who would be the most probable candidates for hormone therapy (HT) for the reduction of menopausal symptoms?
- What if a similar limitation—looking at the effects of HT on women who had reached menopause within the past 5 years—had been imposed?
- What if lower doses of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) had been used?
- What if different estrogens and progestogens had been used?
- What if a different route of HT administration had been used?

Perhaps some or all of the adverse outcomes associated with the use of CEE, alone or with MPA, would have been avoided if an entirely different HT regimen had been used, and if this entirely different HT regimen had been used in women with vasomotor symptoms (VMS) who were, on average, a decade younger than those in the WHI. Of note, the US Food and Drug Administration's labeling for all menopause HT products, including estrogen-progestogen therapy (EPT) combinations and estrogen therapy (ET), is the same even though (1) the populations using these products (ie, nonhysterectomized women and hysterectomized women, respectively)

Received December 8, 2012; revised and accepted October 23, 2013.

From the Department of Obstetrics and Gynecology, George Washington University School of Medicine, Women's Health & Research Consultants, Washington, DC.

Funding/support: Medical writing and editorial support (by Dory Greene; Infor-Med LLC, Warren, NJ) and statistical analysis support (by Howard Hait, MS; Edenridge Associates LLC, Wilmington, DE) were funded by ASCEND Therapeutics (Herndon, VA) and BESINS Healthcare (Bangkok, Thailand).

Financial disclosure/conflicts of interest: J.A.S. has served (within the last year) or is currently serving as consultant to or on the advisory boards of Abbott Laboratories/AbbVie Inc (North Chicago, IL), Agile Therapeutics Inc (Princeton, NJ), Amgen Inc (Thousand Oaks, CA), Apotex Inc (Toronto, Canada), ASCEND Therapeutics, BioSante (Lincolnshire, IL), Depomed Inc (Menlo Park, CA), Everett Laboratories Inc (West Orange, NJ), Intimina by Lelo Inc (San Jose, CA), Lupin Pharmaceuticals (Baltimore, MD), TherapeuticsMD (Boca Raton, FL), Meda Pharmaceuticals Inc (Somerset, NJ), Merck and Co Inc (Whitehouse Station, NJ), Novartis Pharmaceuticals Corp (East Hanover, NJ), Noven Pharmaceuticals Inc (New York, NY), Novo Nordisk (Bagsvrerd, Denmark), Novogyne (East Hanover, NJ), Pfizer Inc (New York, NY), Shionogi Inc (Florham Park, NJ), Shippan Point Advisors LLC (Upper Saddle River, NJ), Slate Pharmaceuticals Inc (Durham, NC), Sprout Pharmaceuticals (Raleigh, NC), Teva Pharmaceutical Industries Ltd (Jerusalem, Israel), Warner Chilcott (Rockaway, NJ), and Watson Pharmaceutical Inc (Corona, CA). He has received (within the last year) or is currently receiving grant/research support from Abbott Laboratories/AbbVie Inc, BioSante, EndoCeutics Inc (Quebec, Quebec), Novo Nordisk, Novogyne, Palatin Technologies (Cranbury, NJ), Teva Pharmaceutical Industries Ltd, and Warner Chilcott. He has also served or is currently serving on the speakers bureaus of Amgen Inc, Eisai Inc (Woodcliff Lake, NJ), Merck and Co Inc, Novartis (Basel, Switzerland), Noven Pharmaceuticals Inc, Novo Nordisk, Novogyne, Shionogi Inc, Teva Pharmaceutical Industries Ltd, and Warner Chilcott. J.A.S. was the chief medical officer for Sprout Pharmaceuticals within the last year.

Address correspondence to: James A. Simon, MD, CCD, NCMP, IF, FACOG, Women's Health & Research Consultants, Suite 450, 1850 M Street, NW, Washington, DC 20036. E-mail: jsimon@jamesasimonmd.com

differ from each other on heart disease risk, osteoporosis risk, and the like; (2) the results of the EPT and ET arms of the WHI differed greatly from each other; and (3) some ETs have little or no systemic absorption.[3] This standard product labeling suggests that all hormonal regimens carry the same risks, which the evidence does not necessarily support.

Since 2002, many retrospective analyses, follow-up studies, and new studies have been conducted to answer these what-if-type questions, particularly the first two questions (see the list above). This report aims to answer the last two questions, which are combined and posed as follows: "What if the WHI had been performed using transdermal estradiol and oral micronized progesterone?" The author considered hypothetical comparisons between oral CEE and transdermal estradiol and between oral MPA and oral micronized progesterone (MP) for their effects on four primary outcomes of the WHI: cardiovascular disease (CVD) risk, cerebrovascular disease (ie, stroke) risk, venous thromboembolism (VTE) risk, and breast cancer (BrCA) risk. Although the discussion in this article focuses on transdermal estradiol delivered through patches, gels, or lotions (these are the most commonly used routes of nonoral estrogen administration), it could be broadened to include all forms of nonoral estrogen administration.

The rationale for using transdermal estrogen instead of oral estrogen is that the first-pass effect associated with oral administration induces many undesirable metabolic effects.[4] These adverse effects include elevated triglycerides (TG), decreased low-density lipoprotein (LDL) particle size, and increased production of some coagulation factors and C-reactive protein (CRP). By contrast, transdermally delivered estrogen does not produce such changes.[4,5] In addition, serum TG levels and thrombotic factors, often increased in women with diabetes mellitus, are not increased further with transdermal HT.[6] Moreover, adverse alterations in blood pressure (BP) in both nonhypertensive and hypertensive women (although considered rare, if not idiosyncratic, reactions) have been reported only with oral therapy. The putative advantage of using MP over MPA is that the former is bioidentical to the body's own progesterone. Recent evidence has shown that natural progesterone displays a favorable action on blood vessels and on the brain, which may not be true for some synthetic progestins.[4] Furthermore, MPA, possibly owing to its glucocorticoid activity, may counteract some of the beneficial effects of estradiol, which is not the case with MP.[4]

Whereas initial concern about the WHI findings focused on CVD and BrCA risks, VTE risk may be of more immediate concern, particularly in younger postmenopausal women who are seeking to initiate HT (either EPT or estrogen alone) for the treatment of menopausal symptoms. Using the concept of attributable risk, the author has provided additional analyses supporting the use of transdermal ET over oral ET, alone or with oral MP, with respect to VTE risk in the postmenopausal population. Similar data on CVD, stroke, and BrCA are not available for this type of analysis; for these outcomes, the author has relied on observational trial data gleaned from large European population studies, without calculation of attributable risk.

BACKGROUND

Findings from observational studies, reviews, and meta-analyses published in the 1990s and early 2000s suggested that postmenopausal HT reduced the risk of coronary heart disease (CHD) and was therefore recommended for primary or secondary CHD prophylaxis in postmenopausal women.[7-10] Offering more support for the cardioprotective effects of HT, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial showed that EPT, compared with placebo, had favorable effects on LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and fibrinogen.[11,12] The two MPA-containing regimens in the PEPI Trial were associated with an increase in 2-hour postload glucose levels compared with placebo, whereas CEE alone and CEE/MP were not.[11] Women in all treatment groups gained weight; the largest weight gain occurred in the placebo group, followed by the CEE/MPA groups and the CEE/MP group. The smallest weight gain occurred in the CEE-alone group ($P = 0.03$ vs placebo).[11,13,14*]

The randomized controlled trial (RCT) HT component of the WHI was initiated based on observational data indicating that estrogen raised HDL cholesterol and reduced LDL cholesterol, which would explain, at least in part, the protective effects of HT on the heart. The unexpected findings of the WHI radically changed physicians' understanding of the benefits and risks of HT. Since the publication of the findings of the CEE/MPA arm in 2002[1] and of the CEE arm in 2004,[2] many investigators have been reevaluating and reanalyzing the WHI findings in an attempt to reconcile them with previous observational study findings.

THE WHI: SUMMARY OF PRIMARY OUTCOMES

The CEE/MPA arm of the WHI was halted after a mean of 5.2 years of follow-up because the rate of invasive BrCA among actively treated participants, compared with placebo recipients, exceeded the stopping boundary for this adverse event (hazard ratio [HR], 1.26).[1] In addition, compared with the placebo group, the CEE/MPA group had excess rates of CHD (HR, 1.29), stroke (HR, 1.41), and pulmonary embolism (PE; HR, 2.13). The CEE-only arm, conducted on hysterectomized

*A transdermal estradiol arm was seriously considered in the planning stages of the PEPI Trial, but resources and support from the transdermal ET manufacturer (Estraderm; Ciba-Geigy Corp, Summit, NJ) were withdrawn when the National Institutes of Health and PEPI investigators determined to make increases in HDL cholesterol the primary end point of the trial (personal communication, Drs. Howard Judd and Robert Langer). According to Langer, "My recollection is that transdermal estradiol was seriously considered but dropped when we determined that, since contrasts between progestogens were a primary aim, the number of participants we could afford to enroll within the budget could support a treatment matrix employing just one estrogen while providing adequate statistical power. Since another major goal was relevance to expected clinical practice when the study was completed roughly 5 years later, we chose the most commonly used estrogen in clinical practice, conjugated equine estrogens. Indeed, the first pass at the study design had about 17 arms that would allow contrasts between virtually all available progestogens, as well as oral and transdermal estradiol, in addition to CEE. The biostatisticians went glassy-eyed, and the project officer reminded us of financial reality." A summary of the PEPI Trial is available.[14]

women, was also terminated early (after a mean follow-up of 6.8 y) because CEE, relative to placebo, did not afford significant cardioprotection (HR, 0.91) and was associated with a significantly increased risk for stroke (HR, 1.39).[2] The BrCA rate was lower in the CEE group than in the placebo group (HR, 0.77), but the rate of VTE, either deep vein thrombosis or PE, was higher (HR, 1.33).

Another way of looking at the WHI data, with a focus on women in their 50s, is to assess the absolute risks for four primary outcomes (CHD, stroke, VTE, and BrCA) in HT users versus placebo users. Figures 1A and 1B depict the increased number of events per 10,000 women per year that occurred with the use of CEE/MPA (EPT arm)[15-18] or CEE alone (ET arm),[2,19-21] respectively, relative to placebo. Figure 2 shows the excess incidence of potentially fatal events attributable to oral CEE in women aged 50 to 60 years.[22]

Because of these findings and the intensive media attention that ensued (much of it reproachful and alarmist), many physicians stopped prescribing HT. Several pharmaceutical companies halted the clinical development of new HT products. Many women stopped using or asking for HT even though moderate to severe VMS and/or vulvovaginal atrophy (VVA) symptoms were diminishing their quality of life. Was this discontinuation or avoidance of HT really necessary for most postmenopausal women? Was it even wise?

As the hand-wringing and the media frenzy subsided, the unexpected findings began to generate investigations of the WHI itself, as well as analyses and reanalyses of its findings and conclusions. With respect to the WHI itself, the main concerns centered on the mean age of the WHI participants (63 y in the CEE/MPA arm and 64 y in the CEE-only arm—markedly older than women enrolled in previous observational trials) and the fact that HT was initiated so many years after these women reached menopause—well past the point when most women seek treatment of VMS and/or VVA symptoms. The other main concern about the WHI was the fact that only one estrogen formulation (oral CEE) and only one progestogen (MPA) were evaluated, each with only one route of administration.[5]

WHY TRANSDERMAL ESTROGEN, ALONE OR WITH MP, MAY BE A BETTER CHOICE

A woman is 51 years old. She has not had a menstrual period in 13 months, and she has been experiencing hot flashes and night sweats of increasing frequency and severity for the past 6 months. She has no contraindications to HT, still has her uterus, and is fully informed about the potential risks and benefits of HT. She asks you whether physicians are still prescribing this treatment to postmenopausal women. You believe that a short course of therapy is in order, but which one? You

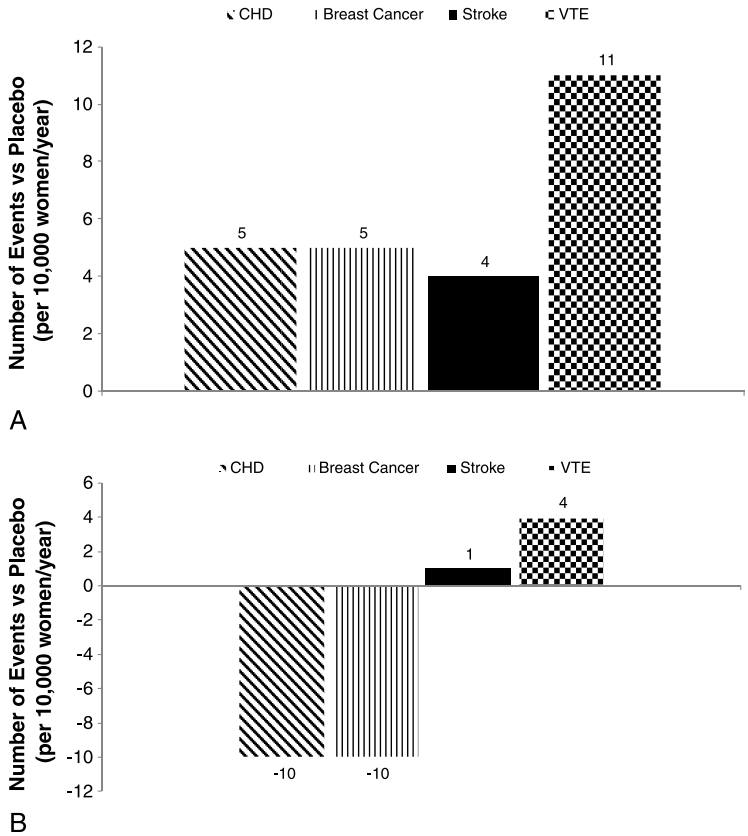

FIG. 1. A: Women's Health Initiative estrogen-progestogen therapy arm. Women aged 50 to 59 years: absolute risks of coronary heart disease (CHD), breast cancer, stroke, and venous thromboembolism (VTE). Modified from Manson et al,[15] Chlebowski et al,[16] Wassertheil-Smoller et al,[17] and Cushman et al.[18] **B:** Women's Health Initiative estrogen therapy arm. Women aged 50 to 59 years: absolute risks of CHD, breast cancer, stroke, and VTE. Modified from Anderson et al,[2] Hsia et al,[19] Hendrix et al,[20] and Curb et al.[21]

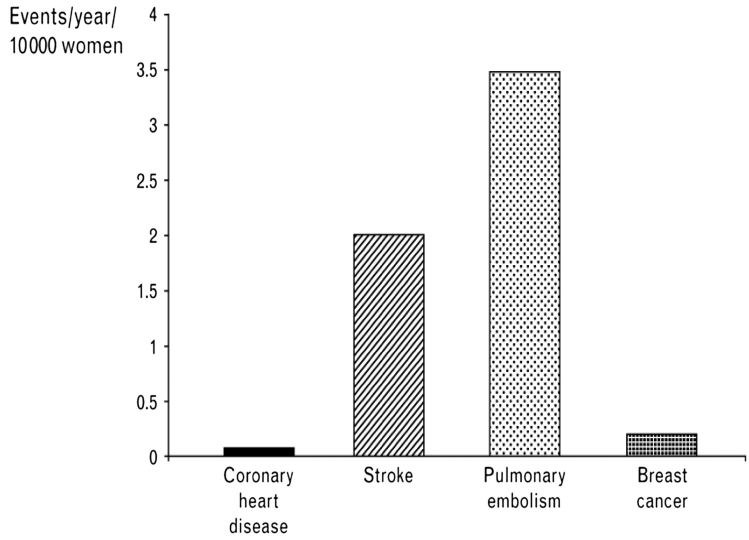

FIG. 2. Excess incidence of potentially fatal events attributable to oral estrogen therapy in both Women's Health Initiative clinical trial arms (combined) among women aged 50 to 59 years. Modified from Olié et al.[22]

just read the report by LaCroix et al[23] in *The Journal of the American Medical Association*, so you feel better about prescribing ET. However, is CEE the way to go? Might a different form of estrogen (eg, transdermal estradiol) be safer? Is there a progestogen (eg, MP) that might be safer than MPA? This article aims to answer these questions.

Cardiovascular disease

According to the National Heart, Lung, and Blood Institute,[24] which amassed data from seven major epidemiologic studies, CVD incidence is 4 cases per 1,000 person-years for women aged 45 to 54 years and 8 to 9 cases per 1,000 person-years for women aged 55 to 64 years. The incidence of CHD alone is 1 to 2 cases per 1,000 person-years in women aged 45 to 54 years and 3 to 6 cases per 1,000 person-years in women aged 55 to 64 years.

Since the publication of the main WHI findings in 2002 and 2004, many authors have performed studies and analyses supporting the timing hypothesis, which states that the unexpectedly adverse CVD-related outcomes would have been mitigated or avoided if WHI participants had started using HT closer to the time of menopause and at an earlier age.[19,25-30] Even in these too-old-for-HT WHI cohorts, follow-up studies showed that the HR for CHD was 0.95 in former CEE/MPA recipients[31] and 0.97 in former CEE recipients[23] 3 years after they stopped their assigned regimen. In the study by LaCroix et al,[23] CVD risk actually declined significantly among women aged 50 to 59 years. In this age group, CHD risk was reduced (HR, 0.59) and myocardial infarction (MI) risk was reduced (HR, 0.54), suggesting that there may be a window of opportunity for safe administration of ET.[32] The timing hypothesis, however, has not been confirmed.[33]

Maybe exogenous estrogen, alone or with a progestogen if needed to protect the uterus, is cardioneutral or even cardioprotective in most postmenopausal women in their 50s. And, maybe, if they desire relief from troublesome VMS and/or VVA symptoms, they may find that, with regard to CVD risk, transdermal estradiol is an even safer choice than oral estrogen and that oral MP is a safer choice than oral MPA. The accumulated evidence to date is convincing. Literature citations that follow include point estimates of relative risk (RR), as reported by the authors. In most cases, these articles also provided 95% CIs for each estimate, giving readers some idea of the variability associated with the findings. For ease of summarizing information as background for the discussion, CIs have been excluded despite their importance to derivation of inferences.

CHD outcomes

In a Danish cohort study, Løkkegaard et al[34] followed approximately 700,000 healthy women aged 51 years or older for 7 years and discovered that nearly 5,000 of these women experienced an MI during this period. Overall, there was no increased risk for MI (RR, 1.03) among current HT users versus never users. The greatest MI risk occurred in continuous HT users; no increased risk was noted in users of unopposed estrogen or cyclic combined therapy. A significantly lower risk for MI was found among transdermal ET users than among oral ET users (RR, 0.77 vs 1.78).

CVD markers and risk factors

Several studies have shown that transdermal ET, relative to oral ET, has more favorable effects (or less deleterious effects) on certain CVD markers, including BP, TG, LDL particle size, coagulation parameters, CRP, and activated protein C (APC).[5,35,36] With regard to progestogens, the PEPI Trial showed that MP, unlike MPA, did not counteract the favorable effects of CEE on HDL cholesterol.[11] Many, if not most, of these markers and risk factors, particularly BP,[37] come into play with regard to stroke risk as well.

Menopause is accompanied by a dramatic rise in the prevalence of hypertension (HTN) in women, suggesting a protective role for endogenous estradiol in BP regulation.[38] Even

small increases in BP are associated with an increased risk for CVD-related events.[38] The following studies ascertained the effects of the estrogen component and/or the progestogen component on BP in postmenopausal women receiving HT:

- Rylance et al[39]: Results of this small, double-blind, placebo-controlled, cross-over study showed that the use of orally administered natural progesterone caused a significant reduction in BP in individuals with mild to moderate HTN who were not using any other antihypertensive medications.
- Hassager et al[40]: This 2-year placebo-controlled study was conducted on 110 early postmenopausal women to examine the effects of percutaneous and oral estradiol, alone or with progestogen, on BP. The investigators found that systolic BP (SBP) and diastolic BP (DBP) remained unchanged in both HT groups, whereas DBP tended to rise in the placebo groups. Both estradiol regimens may have protected against the age-related increase in DBP noted in early postmenopausal women.
- Ashraf and Vongpatanasin[38]: This pooled analysis of large clinical trials showed that oral estrogen, either unopposed or opposed, in postmenopausal women promoted isolated systolic HTN (magnitude of increase, 1-2 mm Hg), whereas transdermal estradiol seemed to have BP-lowering effects.
- Lee et al[41]: In this study, 67 Korean postmenopausal women (mean age, 57 y)—some with HTN and some with normal BP—received CEE, alone or with MP, for 2 months. During daytime, HT use was associated with increased SBP and DBP in normotensive participants and with decreased SBP and DBP in those with HTN. When MP was added to the CEE regimen, the increase in daytime BP among normotensive women was attenuated, and the decrease in daytime SBP in the group with HTN was potentiated.

With regard to diabetes mellitus, which is a major risk factor for CVD, CEE and transdermal estradiol seemed to have had minimal effects on glucose metabolism and insulin resistance, whereas MPA might have had a slightly adverse effect and MP had no adverse effect.[42] The PEPI Trial showed that CEE/MP, unlike CEE/MPA, did not adversely affect carbohydrate metabolism.[11] A recent evaluation of the E3N cohort (E3N is the French component of the European Prospective Investigation into Cancer and Nutrition Study) showed that, overall, the incidence of new-onset diabetes among nearly 64,000 postmenopausal women followed for an average of more than 10 years was lower among HT users than among nonusers (HR, 0.82).[43] In France, the transdermal route of estrogen administration is used far more often than the oral route. For women in this study who used transdermal estrogen plus a progestogen, MP, in a head-to-head comparison with synthetic progestins, had the lowest HR for new-onset diabetes (0.67).[43] A small randomized study by Chu et al[44] showed that, in obese postmenopausal women with metabolic syndrome, insulin resistance and adipocytokine parameters worsened with exposure to oral, but not transdermal, estradiol.

Finally, a nested case-control study using the WHI database showed that although estrogen receptor (ER) polymorphisms were not associated with the risks of vascular events and did not modify the increased risks for CHD, stroke, or VTE related to HT use, a reduced response of plasmin-antiplasmin (a marker of coagulation and fibrinolysis) to HT was noted for ER-1 IVS1 (intron number 1)-354 and ER-1 IVS1-1415.[45] Nevertheless, the authors concluded that screening for ER polymorphisms to identify women at lesser risk for adverse cardiovascular outcomes was not likely to be useful in making decisions about HT use.

Cerebrovascular disease

Among postmenopausal women aged 50 to 59 years, stroke incidence is 6 to 8 cases per 10,000 women per year.[46] Unlike CHD risk, which seems to be attenuated by exogenous estrogen use in women in their 50s, ET-associated ischemic stroke risk, albeit small, seems to rise even in this younger cohort and in older postmenopausal women.[46-48]

Lobo and Clarkson[46] offered a hypothetical explanation for the differential effects of exogenous estrogen on CHD risk (↓) and stroke risk (↑) in 50- to 59-year-olds. Many studies have shown that ET initiated near menopause onset inhibits progression of coronary artery atherosclerosis, presumably via its beneficial effects on lipids and on the endothelium of the coronary arteries. By contrast, delayed ET initiation, particularly in women with established CHD but also in older women who may have undetected atherosclerotic lesions, can have deleterious cardiovascular effects. These authors ascribed the increased ischemic stroke associated with oral standard-dose or high-dose ET to a different disease course (cerebral atherosclerosis develops later than coronary atherosclerosis) and to a different disease process—primary thrombus formation. After all, standard-dose oral ET is associated with an increased risk for thrombus development in the venous circulation not only in younger and older menopausal ET users but also in oral contraceptive (OC) users.

Supporting this hypothesis is the fact that the rate of ischemic stroke risk does not seem to be increased by the postmenopausal use of transdermal estrogen, which does not undergo first-pass hepatic metabolism.[49] In a population-based nested case-control study, a cohort of almost 900,000 women aged 50 to 79 years in the UK General Practice Research Database (recruitment period, January 1987 through October 2006) was identified.[49] During an average of nearly 7 years of follow-up, about 16,000 cases of stroke occurred; these cases were matched to about 60,000 controls in a 1:4 ratio. The adjusted rate ratio of stroke associated with current use of transdermal estrogen, alone or with a progestogen, was 0.95 relative to HT nonuse. Current users of oral estrogen, alone or with a progestogen, had a higher rate of stroke than did HT nonusers (rate ratio, 1.28). Direct comparison between transdermal HT and oral HT showed that stroke risk was significantly lower with the former than with the latter (rate ratio, 0.74).

Venous thromboembolism

The incidence of VTE is 1 to 1.5 per 1,000 person-years in postmenopausal women.[4,50] In addition, VTE is responsible for about one third of potentially fatal CVD-related events in

HT users.[51] It is thought that when oral estrogen undergoes first-pass hepatic metabolism, it increases and modifies globulin synthesis and function, impairing the balance between procoagulant factors and antithrombotic mechanisms.[5,52,53] This phenomenon does not occur with transdermally administered estrogen.[54-56]

In the original WHI reports, the risk for VTE was excessive in both CEE/MPA users (HR, 2.11)[1] and CEE users (HR, 1.33),[2] particularly in the first 2 years of use.[21] Mitigating this early VTE risk would have been highly desirable. Multiple studies conducted during the past decade have indicated that transdermal estrogen is substantially safer than oral estrogen in this regard. No conclusions regarding the possible differential effects of progestogens on VTE risk have been drawn, although some studies suggested that adding MP or MPA to the estrogen regimen did not affect VTE risk, and a recent review suggested that MP was safer than the other progestogens.

ESTHER Study

In the ESTHER (EStrogen and THromboEmbolism Risk) Study, Scarabin et al[57] recruited 155 consecutive cases of a first-documented idiopathic VTE (92 with PE and 63 with deep vein thrombosis) among French postmenopausal women and matched them to 381 controls. The enrollment period covered 1999 to 2002. Compared with ET nonusers, oral ET users had an adjusted odds ratio (OR) for VTE of 3.5 and transdermal ET users had an adjusted OR for VTE of 0.9, indicating that the oral group had nearly a four-times-greater VTE risk than did the transdermal group. The VTE risk for oral HT users increased quickly. The adjusted OR was greatest during the first 12 months of use (10.1) and decreased over time (5.0 after 13-30 mo, 4.0 after 31-48 mo, and 2.5 after >48 mo). By contrast, VTE risk in transdermal HT users was low (1.5, 0.6, 1.3, and 0.9) at these respective checkpoints.

In an extension of the ESTHER Study with an interesting twist (enrollment period, 1999-2004), researchers investigated the impact of the route of estrogen administration on the association between a prothrombotic mutation (factor V Leiden or prothrombin G20210A mutation) and VTE risk.[58] (Of note, prothrombotic mutations are relatively common in the general population; however, several authorities recommend against routine screening for these mutations, except in those persons with a strong personal or family history suggestive of the problem.[59]) Extending recruitment to 235 cases and 554 controls, the investigators found that the factor V Leiden mutation alone was associated with a 3.4-fold increased risk for VTE and that a prothrombin mutation alone was associated with a 4.8-fold increased risk for VTE.[58] Oral estrogen use alone, relative to transdermal estrogen use alone, was associated with a much greater increase in VTE risk (OR, 4.3 vs 1.2). The combination of either one of the prothrombotic mutations and oral estrogen use led to a 25-fold higher risk of VTE (compared with the risk in nonusers without a mutation), whereas the risk for women with a prothrombotic mutation who were using transdermal estrogen was similar to that of women with a mutation who were not using estrogen (respective ORs, 4.4 and 4.1). Unlike oral estrogen, transdermal estrogen did not confer additional VTE risks on women carrying a prothrombotic mutation.

Because oral estrogen use and elevated body mass index (BMI) both increase VTE risk and because prior study data suggested that transdermal estrogen might be safer with respect to thrombotic risk, the ESTHER Study group investigated the impact of transdermal estrogen on the association between overweight/obesity and VTE risk (enrollment period, 1999-2005).[60] Among normal-weight study participants, the ORs for VTE risk were 1.0 for ET nonusers, 1.2 for transdermal ET users, and 5.9 for oral ET users. Among overweight participants, the ORs for VTE risk were 2.7 for ET nonusers, 2.9 for transdermal ET users, and 10.2 for oral ET users. Among obese participants, the ORs for VTE risk were 4.0 for ET nonusers, 5.4 for transdermal ET users, and 20.6 for oral ET users (Fig. 3).[60] Based on these findings, the

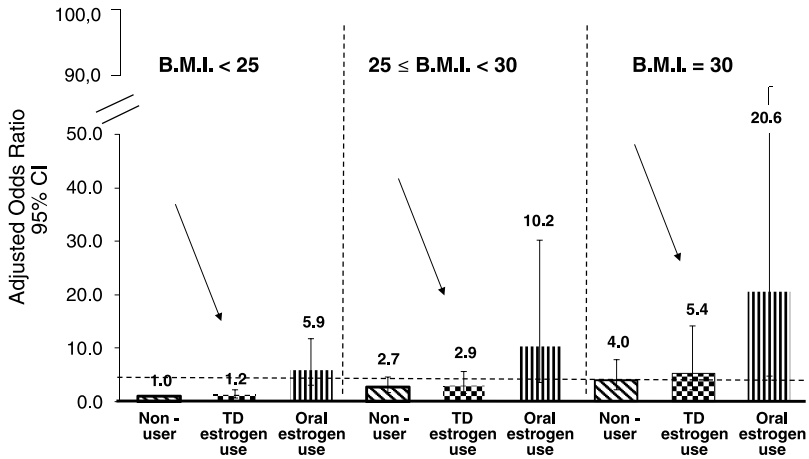

FIG. 3. Venous thromboembolism (VTE) risk in the ESTHER Study: impact of hormone therapy by route of administration (oral estrogen or transdermal [TD] estrogen) and by body mass index (BMI), where a BMI of 30 kg/m^2 or higher represents obesity. Dotted horizontal line indicates the odds ratio of VTE associated with oral estrogen use in the whole population (odds ratio, 4.5; 95% CI, 2.6-7.7). Modified from Canonico et al.[60]

authors concluded that, unlike oral estrogen, transdermal estrogen did not confer an additional risk for idiopathic VTE in women with increased BMI.

The final segment of the ESTHER Study (enrollment period, 1999-2006) focused on the impact of the progestogen component of HT on VTE risk.[61] These investigators recruited 271 consecutive cases with a first-documented episode of idiopathic VTE (208 hospital cases and 63 outpatient cases) and 610 matched controls (426 hospital controls and 184 community controls). Similar to previous studies, the adjusted ORs for VTE in current users of oral or transdermal estrogen versus nonusers were 4.2 and 0.9, respectively. Neither MP nor pregnane derivatives such as MPA or dydrogesterone affected VTE risk (ORs, 0.7 and 0.9, respectively), whereas norpregnane derivatives (nomegestrol acetate and promegestrone) were associated with a nearly fourfold increased VTE risk (OR, 3.9).

Meta-analysis/systematic review

A meta-analysis and systematic review of eight observational studies and nine RCTs derived from an electronic search of 1974-2007 MEDLINE listings was conducted to estimate the risk for VTE in HT users.[62] For the observational studies, oral ET, but not transdermal ET, raised VTE risk. The pooled ORs of first-time VTE were 2.5 in current oral ET users and 1.2 in current transdermal ET users, as compared with ET nonusers. Use of a concurrent progestogen did not affect VTE risk in oral ET users. Results from the RCTs confirmed the elevated VTE risk among oral ET users (OR, 2.1). Among women with a thrombogenic mutation or high BMI, those who used oral ET incurred additional VTE risk, whereas those who used transdermal ET did not.

In an updated meta-analysis, the same group of researchers reviewed six RCTs, five cohort studies, and seven case-control studies for oral ET, as well as four case-control studies and two cohort studies for transdermal ET.[22] The pooled risk ratios for VTE were 1.9 and 1.0 among oral and transdermal ET users, respectively.

An even more recent review by Canonico et al[63] focused on the effects of the different pharmacologic classes of progestogens on VTE risk. The investigators' pooled analysis of data from the ESTHER and E3N Studies suggested that the safest option when adding a progestogen to ET might be transdermal ET combined with MP, although Canonico et al[63] cautioned that RCTs are needed to confirm this result.

Additional studies

Using the same database as in their study on stroke (recruitment was extended to March 1, 2008), Renoux et al[64] identified 23,505 cases of VTE and matched them with 231,562 controls in a nearly 1:10 ratio. VTE risk increased with current use of oral estrogen, alone (rate ratio [RR], 1.49) or with a progestogen (RR, 1.54), but not with current use of transdermal estrogen alone (RR, 1.01) or with a progestogen (RR, 0.96), as compared with HT nonuse.

In the first investigation of the effects of the route of estrogen administration on recurrent VTE risk, Olié et al[50] recruited 1,023 consecutive postmenopausal women aged 45 to 70 years with a confirmed first VTE between January 2000 and December 2008; the women were followed for an average of 79 months after discontinuing anticoagulation therapy. During the follow-up period, 893 women did not use HT and 130 women used HT (most HT regimens contained transdermal estrogen; 10 women used oral estrogen). Recurrent VTE occurred in 77 (7.5%) of the 1,023 women. Transdermal estrogen use, compared with HT nonuse, conferred no additional risk for recurrent VTE (HR, 1.0), whereas oral estrogen use increased this risk by 6.4-fold. Among transdermal estrogen users, concurrent use of MP did not alter recurrent VTE risk. By contrast, use of a norpregnane derivative with transdermal estrogen increased the risk by 4.7-fold.

In an editorial accompanying the study by Olié et al,[50] Lobo[53] acknowledged its unusual nature (HT is generally contraindicated in women with prior VTE) and the small numbers (two VTE cases among 10 oral HT users and six VTE cases among 103 transdermal HT users). Nevertheless, Lobo[53] thought that these findings supported the notion that, with regard to thrombotic risk, transdermal estrogen is safer than oral estrogen, at least in standard doses.

North American researchers, using a prescription database of almost 55,000 women from 2002 to 2009, conducted a retrospective matched-cohort comparison of the incidence of reported VTE among users of transdermal estradiol therapy versus oral ET (approximately 27,000 women per group).[65,66] VTE developed in 115 transdermal estradiol users versus 164 oral estrogen users (adjusted incidence rate ratio [aIRR], 0.67), which is a significant difference. The incidence rate reduction among transdermal estradiol users versus oral estrogen users was even greater for VTE-related hospitalization (aIRR, 0.38) and PE (aIRR, 0.46), the most serious type of VTE event. Although somewhat limited by uncertainties associated with risk factors, the underlying expected rate of VTE in the participant population, classification of VTE events, and the potential for study participants to have received various products at various strengths for various periods of time, these real-world results are consistent with those of European case-control studies conducted to date.

The first ever case-control study was conducted to compare the effects of OCs versus HTs, either oral or nonoral, on VTE risk in women older than 50 years.[67] For the 1,082 women with a first VTE and 1,468 controls included in the study, the ORs for VTE were 6.3 in OC users, 4.0 in oral HT users, and 1.1 nonoral HT users, demonstrating a pattern seen in the ESTHER Study reported 9 years previously.

Finally, Sweetland et al[68] linked the records of more than 1 million UK postmenopausal women to the records of routinely collected hospital admissions and deaths, with a focus on HT use and VTE. During 3.3 person-years of follow-up, 2,200 women experienced a VTE that was diagnosed an average of 1.5 years after last reporting HT use. RRs in current users versus never users were significantly higher for oral EPT than for oral ET (2.07 vs 1.42), with no increased risk for transdermal ET (0.82).

Underlying mechanism for the difference between HT administration routes

Many studies have been conducted to elucidate the mechanisms underlying the differential effects of oral and transdermal estrogens on VTE risk. Post et al[55] ascertained whether the effects of oral ET differed from those of transdermal ET with regard to resistance to APC (an important risk factor for venous thrombosis) and levels of related proteins (eg, protein S, protein C, and prothrombin). The research team observed increases in APC resistance that were more pronounced in oral ET groups than in a transdermal ET group. For nonhysterectomized women, what might be the effects of adding a progestogen? Oger et al[56] found that transdermal ET, when combined with oral MP, did not induce APC resistance, whereas Canonico et al[69] found that transdermal ET plus a norpregnane derivative did induce APC resistance.

Bagot et al[52] compared oral and transdermal HTs with respect to thrombin generation, a marker of hypercoagulability. They found that thrombin generation was significantly increased in oral HT users, but not in transdermal HT users. They surmised that this effect was probably mediated by the hepatic first-pass metabolism of estrone (the main metabolite of oral estradiol), which is avoided by the transdermal route.

Breast cancer

One in eight women will develop BrCA in her lifetime.[70] Even though a woman is much more likely to develop and die of CVD than BrCA (in 2007, 306,000 women died of heart disease and 41,000 women died of BrCA[71]), the latter disease is more feared[72,73] and is more likely to affect attitudes toward HT risks/benefits and use.[74,75]

Although endogenous estrogen exposure has been associated with BrCA, a cause-and-effect relationship between exogenous estrogen use and BrCA has not been established.[4,5,73,76] After all, women in the WHI CEE-alone arm had no increased BrCA risk (HR, 0.77)[2] even after a mean postintervention follow-up of 4 years (HR, 0.77).[23] That being said, because BrCA risk was elevated in CEE/MPA users (HR, 1.26), did the progestogen component (MPA) somehow play a role in increasing BrCA risk?

Role of progestogen

Findings from a large clinical trial suggested that two progestogens were safer than others in relation to BrCA risk.[77] Using data from the French E3N cohort study, Fournier et al[77] assessed the association between different HTs and BrCA risk. During a mean follow-up of 8.1 years, 2,354 cases of invasive BrCA were identified among 80,377 postmenopausal women. Among hysterectomized women, compared with HT never users, estrogen users had a 1.29-fold increased risk for BrCA. Route of estrogen administration did not affect BrCA risk (RRs, 1.32 for oral estrogen and 1.28 for transdermal/percutaneous estrogen). For nonhysterectomized women, the RRs for BrCA were 1.00 for estrogen/MP users, 1.16 for estrogen/dydrogesterone users, and 1.69 for estrogen/other progestogen users (these progestogens had androgenic, nonandrogenic, or antiandrogenic activity and did not differ significantly from one another in terms of their effects on BrCA incidence). The investigators concluded that the choice of the progestogen component may influence BrCA risk, with MP or dydrogesterone being safer than other progestogens.

Using data from the E3N cohort to answer a different question (Does the relationship between HT use and BrCA risk vary according to the gap time between menopause onset and treatment initiation?), Fournier et al[78] found that, among recent HT users, BrCA risk varied according to the timing of treatment initiation. When initiated close to the time of menopause, HT use (estrogen plus any type of progestogen) was associated with an increased BrCA risk. However, this finding pertained only to short durations of HT use (≤2 y): the HR was 1.54 for short treatments initiated in the 3-year period after menopause onset but was only 1.00 for short treatments initiated later on. This pattern of risks was not observed in users of estrogen/progesterone; this group had no significantly increased BrCA risk associated with short duration of use (HRs, 0.87 for treatments initiated ≤3 y after menopause and 0.90 for treatments initiated later on). This seemingly protective effect of progesterone did not apply to other progestogens. Short durations of estrogen/dydrogesterone use were associated with an HR of 1.44 for gap times of 3 years or less and an HR of 1.14 for longer gap times. Short durations of use of estrogens plus other progestogens were associated with an HR of 1.89 for gap times of 3 years or less and an HR of 1.02 for longer gap times.

Progestogens differ widely in their chemical structures, structure-function relationships, metabolism, pharmacokinetics, and potencies; it is reasonable to expect them to exert different effects on breast tissue.[77,79,80] Data from animal studies and in vitro studies have provided clues to the biological plausibility of these differences.[81,82]

Possible role for the route of estrogen administration

Although the E3N European Prospective Investigation into Cancer and Nutrition Study cohort showed no difference between oral and transdermal/percutaneous estrogen in relation to their effects on BrCA risk, a randomized study conducted on 202 postmenopausal women showed that use of transdermal HT, relative to that of oral HT, was associated with a significantly lower mean breast density at the end of the study (38.4% vs 46.9%).[83] Study participants had received transdermal or oral estradiol/norethindrone acetate for 1 year.

Elaborating on the main results, the investigators reported that 35.3% of women in the oral HT group, but only 12.6% of women in the transdermal HT group, had a moderate or marked increase in breast density (≥15%).[83] Moreover, only 15.7% of oral HT users, versus 39.1% of transdermal HT users, had no change in breast density. Degree of breast tenderness correlated positively with increases in mammographic breast density. Changes in mammographic breast density with the different HT regimens may reflect different associations with BrCA risk; the jury is still out in this regard. At the very least, transdermal HT, as compared with oral HT, may improve quality of life by diminishing breast tenderness.

Estrogens trigger both the proliferation of normal breast epithelial cells and the progression of BrCA cells.[5] Other mechanisms related to estrogen metabolism may come into play with regard to carcinogenesis. In particular, certain estradiol metabolites have been found to have antiproliferative and antiangiogenic properties[84] and may distinguish between the effects of oral and transdermal estrogens on breast tissue.[85,86]

Putting it all together

A recent study of 77 healthy postmenopausal women showed that the regimen used in one arm of the WHI, namely, CEE/MPA, had an adverse impact on breast cell proliferation, whereas the regimen advocated in this article, namely, transdermal estradiol/MP, did not.[87] Participants were randomized to receive sequential HT with conventional oral CEE/MPA or with natural estradiol gel/oral MP, with the progestogen being given on days 14 to 28 of each cycle. Two percutaneous stereotactic core-needle biopsies were performed before treatment and during one of the last 3 days of the second 28-day treatment cycle. For 2 months, treatment with CEE/MPA induced a highly significant increase in breast cell proliferation (from a mean of 1% at baseline to a mean of 10.0%), whereas treatment with percutaneous estradiol/oral MP did not (corresponding means, 3.1% and 5.8%). It is not known whether the estrogenic or progestogenic component of HT, or a synergy between the two, led to the more beneficial effects with the use of percutaneous estradiol and oral MP.

HOW IS RISK EVALUATED AND COMMUNICATED?

Attributable risk versus RR

Most studies reviewed in this article used RR reduction as an indicator that transdermal HT may be preferred to oral HT, particularly within the context of VTE risk. Yet even before the publication of the initial WHI findings in 2002 and 2004, Santen and Petroni[88] had provided a comprehensive discussion of the limitations of using RR alone as a measure of the potential harm or benefit of ET. Difficulty in understanding the meaning and implications of RR was considered more extensively after the WHI results were publicized,[73] particularly as a response to the various media citations of risk estimates, many of which were not properly explained or were presented out of context.

Beyond RR and of equal or greater importance when interpreting studies such as the WHI is the excess risk (ie, the attributable risk) associated with using HT versus not using HT or, in the case of this review, using transdermal HT versus using oral HT, each as compared with not using HT. That is, to what extent does an RR higher than 1 translate into the actual number of women who could expect to be affected by the risk factor of value (in this situation, by the exposure to HT)? Answering this question, especially in light of what should be regarded as small departures from an RR of 1 (in either direction) seen in both the WHI and the other studies highlighted, is important.

RR is simply a ratio of the probabilities of the incidence of an outcome event (eg, VTE) for individuals exposed to the risk factor of interest (eg, use of an HT product) compared with those individuals who are not exposed to this risk factor (eg, nonuse of this HT product or use of a different HT product). RR is not a function of the actual number of women in the population who use a particular HT product, nor does it depend on one's knowledge of the actual prevalence or extent of the risk factor in the target population (eg, the proportions or numbers of women actually using transdermal or oral HT). These attributes make RR a portable measure that can be calculated across studies of varying designs and target populations, with the principal aim of demonstrating the consistency and reproducibility of an observed finding.

However, depending on the outcome in question, the magnitude of RR may have little to do with the actual number of women who might be affected. A small RR could have strong clinical relevance if the number of women exposed to the risk factor of interest is indeed large. By contrast, a large RR means little if the actual number of persons who would be affected is also small owing to the small number of exposed participants.

The problem is even more evident considering that, among HT users, the frequency of the use of oral products in the United States (about 80%) has historically been much greater than that of transdermal products (about 20%). This difference complicates the understanding of RR for real numbers of women who may be affected by a certain risk. On the other hand, attributable risk becomes difficult to evaluate even in light of what could be a large RR because the number of women exposed to transdermal HT versus oral HT is considerably smaller. Yet this balancing of both RR and attributable risk (actually, the population attributable risk [PAR]) is the cornerstone of a meaningful understanding of the risk/benefit evaluation of HT in general and—in the case of all other risk factors being equal—the contention of some authors that, for example, the VTE risk for transdermal HT is less than that for oral HT when both are compared with HT nonuse.

In an attempt to provide at least a foundation for such a discussion, the basic estimates of PAR[89,90] were calculated using three case-control studies that focused on VTE risk. Although this review has touched on a number of outcome measures for which transdermal HT has been evaluated in comparison with oral HT, the current understanding of VTE risk attributable to oral HT is based on the biologically plausible concept that first-pass liver metabolism of oral estrogens results in dose-dependent increases in liver-dependent clotting factors, giving rise to greater coagulability. As a result, the most complete source of data in the literature involves VTE outcomes.

Analysis of the PAR of VTE for transdermal versus oral HT

Methods

The studies reported by Canonico et al[61,91] and Renoux et al[64] were considered good examples of investigations that specifically presented data on transdermal versus oral HT use with respect to VTE risk. Each study used information from a separate database, although the two more recent studies

incorporated substantially larger sample sizes than did the earliest study. In addition, Renoux et al[64] took into consideration the use or nonuse of a progestin within the oral or transdermal HT regimen. Canonico et al[91] provided some data on various progestin combinations, but the use of progestins was not reported separately for oral and transdermal HT.

The data sets used in all three of these studies were drawn from populations in Western Europe, where transdermal HT use is much more prevalent than in the United States, where the WHI was conducted. However, the ages of participants considered in each of the three studies were consistent with the original WHI age range of 50 to 79 years at entry. Some differences are unavoidable because the WHI was a prospectively defined study, whereas the three European studies considered for the PAR calculations were all retrospective case-control investigations. Canonico et al[61] included women with a mean age at menopause of approximately 49 years who had a mean age of almost 62 years at the time case records were obtained. Canonico et al[91] highlighted a participant population with a mean age of 54 years at study entry and an average of 10 years of follow-up for data collection. Renoux et al[64] specifically drew records for women aged between 50 and 79 years during a stated calendar period between January 1987 and March 2008.

The RCT design is considered the gold standard for evaluating differential treatment effects. To date, however, many of the published studies evaluating the risks associated with transdermal HT have been performed in an observational setting or a case-control setting; the smaller number of women on transdermal HT than on oral HT has made an RCT of transdermal HT similar in magnitude to the WHI virtually impossible. Fortunately, both the observational and case-control studies used in this review incorporated large sample sizes. These studies may not be representative of either the global population at risk for VTE or, in particular, the US population. Nonetheless, these studies provide at least some insights into the potential risk for VTE as a function of method of HT administration.

The intent of this analysis was to quantify potential changes in excess risk associated with transdermal versus oral HT—not to determine whether such risk was or was not statistically significant based on statements surrounding statistical power and pooling of data to achieve a critical sample size for analysis. Therefore, each of the three studies was considered an independent assessment of VTE risk. A pooled data approach, such as that used in the Canonico et al[62] meta-analysis for estimating RR, was not considered in the estimation of PAR because of differences in design, target population selection, and relative numbers of cases and controls among the three studies.

Attributable risk is defined as that proportion of a population where an outcome is present such that, if the exposure factor of interest could be eliminated, the rate of occurrence of the outcome of interest would be reduced. Although the outcome of interest is assumed to be a consequence of exposure, this outcome will also inevitably be present in a certain proportion of the exposed population wherein exposure did not play a part. Therefore, PAR becomes useful for evaluating the contribution of a risk factor among all persons in the population who have the disease or condition undergoing study, not just those who were exposed to the risk factor. However, because PAR is dependent on the rate of exposure of the risk factor in the population, its utility as an index becomes limited if this rate is either unknown or varies among study populations.[89]

In a case-control study, where the rate of exposure in the population is almost surely unknown, methods have been developed to estimate PAR under a special set of assumptions.[89] In particular, if the rate of occurrence of the outcome (in this case, VTE) is low and the control group used in the study represents what would have been a random sample from the target population, OR can be considered a reasonable estimate of RR, and PAR (call it PAR_{cc}) can be calculated as:

$$PAR_{cc} = \frac{[P(\text{HT users among all cases}) - P(\text{HT users among all controls})]}{[1 - P(\text{HT users among all controls})]}.$$

Results

Data from the study by Canonico et al[61] yielded the results presented in Table 1. Table 2 lists the results gleaned from the study by Canonico et al.[91] Findings from the study by Renoux et al[64] are presented in Table 3.

Discussion

In all three studies, results showed that transdermal HT was associated with a modestly reduced PAR of VTE versus oral HT, when compared with HT nonuse. The studies by Canonico et al[91] and Renoux et al[64] produced similar estimates of RR (about 40% greater for oral HT compared with transdermal ET); however, the transdermal HT PAR estimate

TABLE 1. *VTE risk in a study by Canonico et al*

Mode of delivery		Use of ET	Nonuse of ET	Total	Proportion	Simple odds ratio	PAR_{cc}	PAR_{cc} 95% CI
Oral	Cases	45	146	191	0.2356	3.03	0.159 (1,590 of 10,000)	0.083 to 0.226
	Controls	39	384	423	0.0922			
Transdermal	Cases	67	146	213	0.3146	0.98	−0.0059 (−59 of 10,000)	−0.121 to 0.096
	Controls	180	384	564	0.3191			

VTE, venous thromboembolism; ET, estrogen therapy; PAR, population attributable risk.

Adapted from Table 2 in a study by Canonico et al[61] with permission from Wolters Kluwer Health. Copyright © 2007, American Heart Association, Inc. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

TABLE 2. *VTE risk in another study by Canonico et al*

Mode of delivery		Use of ET	Nonuse of ET[a]	Total	Proportion	Simple odds ratio	PAR_{cc}	PAR_{cc} 95% CI
Oral	Cases	81	181	262	0.3092	1.40	0.088 (880 of 10,000)	0.011 to 0.159
	Controls	93,120	291,218	384,338	0.2423			
Transdermal	Cases	174	181	355	0.4901	1.04	0.020 (200 of 10,000)	−0.085 to 0.115
	Controls	268,307	291,218	559,525	0.4795			

VTE, venous thromboembolism; ET, estrogen therapy; PAR, population attributable risk.
[a]Uses person-years of exposure.
Adapted from Table 2 in a study by Canonico et al[91] with permission from Wolters Kluwer Health. Copyright © 2010, American Heart Association, Inc. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

of 200 of 10,000 in the study by Canonico et al,[91] as opposed to the other two studies, suggested at least some degree of VTE risk for transdermal HT administration. However, this risk estimate did represent a reduction potential of almost 700 VTE cases per 10,000 women compared with oral HT. By contrast, transdermal HT use in the studies by Canonico et al[61] and Renoux et al[64] showed, in essence, no PAR associated with therapy (PARs of −59 of 10,000, 3 of 10,000, and −5 of 10,000, respectively).

In the study by Renoux et al,[64] the PAR differential for oral HT was between 100 and 200 women per 10,000 women, compared with transdermal HT. In and of itself, this number is minimal but should be interpreted in light of the absence of VTE risk associated with transdermal HT in those studies. Of note, the PAR calculations obtained by the stated formula do not differ much from the simple difference in risk proportions that would have been used to estimate PAR if these had been prospective cohort studies (eg, in Table 3, 0.0354 − 0.0247 = 107 of 10,000, compared with 111 of 10,000 for the oral ET users).

Whereas the respective RR estimates for oral EPT and patch EPT use in Renoux et al[64] were smaller than those for their ET counterparts, the increase in PAR between oral EPT and patch EPT users (approximately 210 of 10,000 women) is greater than the corresponding ET comparison (approximately 108 of 10,000 women). One might speculate that any excess VTE risk associated with the use of oral HT is exacerbated when the oral product is a combined EPT preparation or when estrogen-only oral administration is combined with, or followed by addition of, a progestin. Such an observation based on PAR is made despite what, at least on inspection, seems to be little difference in RR (1.45 vs 1.39) between estrogen-only therapy and oral EPT. The studies by Canonico et al[61,91] did not differentiate progestin use between oral and transdermal HT and could therefore not be used to either support or refute this contention.

The results seen in the study by Renoux et al[64] help explain the difficulty in interpreting RR without also calculating PAR. Because no standard or other clinical guidelines for assessing the difference in the various RR estimates have been posited, one would have difficulty in clinically assessing the meaning of differences among the various RR estimates other than to say that they all either point in the same direction or they do not. However, one can render clinical judgment as to whether an increase or a decrease in the actual number of exposed individuals who exhibit a particular clinical outcome is an indication of something worth considering and even looking into further. There is also the additional chance that RR and PAR calculations could lead to conflicting inferences. For example, the PAR oral HT estimates in Table 3 reflect a reversal in direction from the RR estimates, making interpretation of risk assessment somewhat less clear; whereas the RR for oral EPT is slightly smaller than the RR for oral ET, the PAR for oral EPT is almost twice the PAR for oral ET.

Results of the study by Canonico et al[61] are of interest because they are based on a much smaller group of women than the other two studies. This study had an oral HT use versus HT non-use OR greater than 3, with an associated PAR of VTE of almost 1,600 per 10,000 women treated, versus no

TABLE 3. *VTE risk in a study by Renoux et al*

Mode of delivery		Use of ET	Nonuse of ET	Total	Proportion	Simple odds ratio	PAR_{cc}	PAR_{cc} 95% CI
ET oral	Cases	729	19,849	20,578	0.0354	1.45	0.0111 (111 of 10,000)	0.008 to 0.014
	Controls	5,105	201,985	207,090	0.0247			
ET patch	Cases	273	19,849	20,122	0.0136	1.02	0.0003 (3 of 10,000)	−0.001 to 0.002
	Controls	2,721	201,985	204,706	0.0133			
EPT oral	Cases	1,277	19,849	21,126	0.0643	1.39	0.0210 (210 of 10,000)	0.014 to 0.020
	Controls	9,342	201,985	211,327	0.0442			
EPT patch	Cases	92	19,849	19,941	0.0046	0.90	−0.0005 (−5 of 10,000)	−0.002 to 0.000
	Controls	1,043	201,985	203,028	0.0051			

VTE, venous thromboembolism; ET, estrogen therapy; PAR, population attributable risk; EPT, estrogen-progestogen therapy.
Adapted from Table 2 in a study by Renoux et al[64] with permission from John Wiley and Sons. Copyright © 2010, International Society on Thrombosis and Haemostasis. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

excess risk for transdermal HT users. That this excess risk differs substantially from that found in the other larger studies may be a function of participant selection (eg, large national databases with more diverse and varied distributions of clinics and participants, as opposed to a much smaller, more localized setting of hospitals within France).

Although the results of the study by Canonico et al[61] suggested that use of transdermal HT, versus oral HT, was associated with a lower VTE risk, it remains difficult to determine the true implication of that reduced risk on the number of women in the target population who would consider using transdermal HT. It is equally difficult to estimate the number of women requiring EPT who would also reduce their VTE risk by using a transdermal product, although the results of the studies by Canonico et al[61] and Renoux et al[64] suggest a lack of excess VTE risk above and beyond that expected in the greater population of HT nonusers.

One further observation concerns the differences in absolute rates of VTE risks calculated in the three case-control studies, as compared with risks based on prospective findings shown in the WHI. Whereas the case-control studies convey the same message as the WHI (that VTE risk seems to be higher among users of oral HT than among users of transdermal HT), it is difficult to draw comparisons between the WHI and the case-control investigations with respect to the number of women using transdermal HT for whom the reduction in VTE risk would be expected. Variations in study design, participant populations, and the manner in which the various expressions of risk are calculated all contribute to this problem. Although a more realistic, population-based estimate of the number of women for whom transdermal HT might be the more favorable option cannot be easily obtained, the results are suggestive of a clinically relevant outcome that would become more noticeable by prescribers and women as the prevalence of transdermal HT use increases.

SOCIETY GUIDELINES

Four societies, including The North American Menopause Society, the European Menopause and Andropause Society, the Endocrine Society, and the International Menopause Society, have recently issued guidelines regarding the use of HT.[6,29,59,92,93] Important comments and recommendations include the following.

Cardiovascular disease

- According to the most recent position statement of The North American Menopause Society,[6] HT initiation by women aged 50 to 59 years or by women within 10 years of menopause to treat typical menopause symptoms does not seem to increase the risk of CHD events. In fact, emerging evidence indicates that initiation of HT in early postmenopause may reduce CHD risk.
- Adverse BP alterations in women with or without HTN have been reported only with oral HT.[6]
- Nonoral routes of HT administration, including transdermal and intrauterine systems, may offer both advantages and disadvantages compared with the oral route, but the long-term benefit-risk ratio has not been demonstrated.[6] Differences would be related to the role of first-pass hepatic metabolism, the hormone concentrations in the blood achieved by a given route, and the biological activity of the ingredients. With transdermal therapy, there were no significant increases in TG, no changes in CRP, no increases in sex hormone–binding globulin, and few effects on BP.
- For relief of troublesome VMS and/or VVA symptoms, transdermal HT is the first choice among women at increased risk for CHD and among those with preexisting diseases.[29] The rationale for this recommendation is the lesser effect of transdermal HT versus oral HT on coagulation parameters.

Cerebrovascular disease

- Oral ET and oral EPT increase the risk for ischemic stroke by about one third in relatively healthy postmenopausal women.[92] In a large observational study, transdermal estradiol at a dose of 50 μg or less did not increase stroke risk.[49,92]

Venous thromboembolism

- Growing evidence suggests that women with a history of VTE and women with a factor V Leiden mutation are at increased risk for VTE with HT use. Limited observational data suggest lower VTE risk with transdermal versus oral ET, but no comparative RCT data are yet available.[6]
- Serum TG levels and thrombotic factors, often increased in persons with diabetes, are not increased further with transdermal HT use.[6]
- Transdermal estrogen does not increase venothrombotic episode risk (level of evidence C).[93]
- Although no RCTs assessing transdermal estrogens with respect to VTE risk have been conducted, numerous epidemiologic and biological data suggest that transdermal estrogen is safer than oral estrogen.[59] Transdermal HT should be the first choice in overweight/obese women.[59]
- A personal history of VTE and, in some cases, a family history of VTE (if associated with a prothrombotic mutation) are strong contraindications to oral HT. When HT is required, transdermal estrogen can be considered after careful individual evaluation of benefits and risks.[59]
- In managing postmenopausal women with a personal or family history of VTE, MP or dydrogesterone is the preferred progestin for nonhysterectomized women.[59]

Breast cancer

- Early data from a large observational trial suggest that an HT regimen containing MP may not be associated with an increased risk for BrCA if it is used for up to 5 years; these findings require confirmation.[6]
- Several studies have shown that MP has an overall better risk profile than do other progestogens with regard to both thrombotic and BrCA risks. Therefore, in women who

require uterine protection, MP in combination with transdermal estrogen is preferred.[59]

FINAL COMMENT

One consequence of the WHI reports in 2002[1] and 2004[2] was the precipitous decline in the use of HT, including ET in hysterectomized women.[94] From 2001 to 2009, HT use by women in their 50s declined by 60%.[94] This reduced use of HT may have had unforeseen and unintended consequences for women in their 50s: When data from the two WHI reports were combined, mortality was found to be 30% lower in HT users versus nonusers.[27] Similarly, the postintervention follow-up of WHI participants by LaCroix et al[23] showed that women in their 50s who were randomized to CEE, as compared with women randomized to placebo, had a 27% lower risk of death, which translated into 13 fewer deaths per 10,000 person-years. Sarrel et al[95] derived a formula to relate the excess mortality found among hysterectomized women aged 50 to 59 years who were assigned to placebo in the WHI to that of the entire population of comparable US women, while also incorporating the decline in ET use observed between 2002 and 2011. They found that a minimum of 18,601 postmenopausal women and a maximum of 91,610 postmenopausal women died prematurely because of ET avoidance. Considering the mortality data for women in this age bracket in the WHI reports and in the follow-up studies by LaCroix et al[23] and Hodis,[96] the findings reported by Sarrel et al[95] are not surprising. However, they do raise the specter of whether a lack of appropriate HT use contributes to rising female mortality rates in almost half of US counties.[96]

CONCLUSIONS

Although some experts have called for an independent commission to scrutinize every major WHI article and to determine whether the data justified the conclusions drawn,[97] this author posed a simple and focused question: What if the WHI had been performed using transdermal estradiol plus MP in women who need uterine protection? The findings probably would have been quite different from those initially reported in 2002[1] and 2004.[2] In fact, the data suggest that women treated with transdermal estradiol (instead of CEE) and with oral MP (instead of MPA) would probably have fared better with regard to CVD risk, stroke risk, VTE risk, and BrCA risk. This conclusion is based on a review of the recent literature presented here, with a specific focus on studies dealing with VTE risk. No RCTs of the magnitude of the WHI have been conducted during the past decade, so the conclusions about CVD, cerebrovascular disease, and BrCA risks are drawn mainly from observational data derived from large European population studies. Likewise, the effects of oral versus transdermal ET on VTE risk must be tested in an RCT before one can reach conclusions about superiority.[30]

Although low to begin with, CVD and stroke risks—particularly in women in their 50s—would have been mitigated or eliminated by switching from CEE to transdermal estradiol, according to the results of two major studies.[34,49] In addition, many other studies have supported the superiority of transdermal estradiol to oral estrogen for reducing CVD markers and risk factors.[5,35,36,44] A large clinical trial conducted by Fournier et al[77] showed that BrCA risk would have been reduced if women had used MP instead of MPA. RCTs are still needed to test and confirm all these findings; in the meantime, additional observational data are welcome but not yet available.

Among all the risk factors studied, the assessment of VTE risk (the greatest risk factor for early postmenopausal women) has incorporated the most extensive database for the evaluation of both RR and PAR. To that extent, the three studies used in this analysis of PAR provide a good foundation for initial findings that transdermal HT may be preferable to oral HT for the treatment of postmenopausal symptoms, with all other risk factors being equal.[61,64,91] Nevertheless, a prospective RCT would be the best method for confirming this hypothesis. The National Institutes of Health has shied away from such an investigation for a variety of reasons, not the least of which is cost. However, within the context of the population at risk, the rate of VTE may be too small for such a study to be practical.

Although physicians should seek to minimize any excess VTE risk when prescribing HT, they should also consider the risk of VTE occurring both in the study and in the general population. The growing obesity epidemic and its inherent risk of thrombosis in this population may be just such an example.[60] In this context, case-control investigations, such as those presented in this review, may play a prominent role in decision-making regarding which method of HT administration is optimal for a particular woman. PAR estimates from the three case-control studies presented here suggest the tenability of a clinical outcome supporting a reduced number of VTE cases when using transdermal HT versus oral HT. The consistency of the three study results provides even greater support for that conclusion.

REFERENCES

1. Rossouw JE, Anderson GL, Prentice RL, 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;288:321-333.
2. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-1712.
3. Vagifem [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; 2003-2010. Available at: http://www.novo-pi.com/vagifem.pdf. Accessed November 28, 2012.
4. L'Hermite M, Simoncini T, Fuller S, Genazzani AR. Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review. *Maturitas* 2008;60:185-201.
5. Modena MG, Sismondi P, Mueck AO, et al. New evidence regarding hormone replacement therapies is urgently required transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. *Maturitas* 2005;52:1-10.
6. The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17:242-255.
7. Rijpkema AH, van der Sanden AA, Ruijs AH. Effects of post-menopausal oestrogen-progestogen replacement therapy on serum lipids and lipoproteins: a review. *Maturitas* 1990;12:259-285.

8. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;20:47-63.
9. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016-1037.
10. 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.
11. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199-208.
12. Barrett-Connor E, Slone S, Greendale G, et al. The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women. *Maturitas* 1997;27:261-274.
13. Espeland MA, Stefanick ML, Kritz-Silverstein D, et al. Effect of postmenopausal hormone therapy on body weight and waist and hip girths. Postmenopausal Estrogen-Progestin Interventions Study Investigators. *J Clin Endocrinol Metab* 1997;82:1549-1556.
14. Langer RD. Postmenopausal Estrogen/Progestin Interventions Trial (PEPI). In: D'Agostino RB, Sullivan L, Joseph Massaro J, eds. *Wiley Encyclopedia of Clinical Trials*. Hoboken, NJ: John Wiley and Sons, Inc, 2008.
15. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-534.
16. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-3253.
17. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673-2684.
18. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573-1580.
19. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006;166:357-365.
20. Hendrix SL, Wassertheil-Smoller S, Johnson KC, et al. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* 2006;113:2425-2434.
21. Curb JD, Prentice RL, Bray PF, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772-780.
22. Olié V, Canonico M, Scarabin PY. Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. *Curr Opin Hematol* 2010;17:457-463.
23. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305-1314.
24. National Heart, Lung, and Blood Institute (NHLBI). Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases. Available at: http://www.nhlbi.nih.gov/resources/docs/06a_ip_chtbk.pdf. Accessed November 28, 2012.
25. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. *J Womens Health (Larchmt)* 2006;15:35-44.
26. Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report: Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. *J Gen Intern Med* 2006;21:363-366.
27. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-1477.
28. Hodis HM. Assessing benefits and risks of hormone therapy in 2008: new evidence, especially with regard to the heart. *Cleve Clin J Med* 2008;75:S3-S12.
29. Schenck-Gustafsson K, Brincat M, Erel CT, et al. EMAS position statement: managing the menopause in the context of coronary heart disease. *Maturitas* 2011;68:94-97.
30. Taylor HS, Manson JE. Update in hormone therapy use in menopause. *J Clin Endocrinol Metab* 2011;96:255-264.
31. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036-1045.
32. Baber RJ. Health outcomes in postmenopausal women with prior hysterectomy after stopping CEE therapy. *Menopause Live*. IMS Updates. May 9, 2011. Available at: http://www.imsociety.org/updates_view_open.php?menopauseliveID=1165&SESSID=7o617501sipnf6gjjpjblsa2h1.
33. Fournier A. Should transdermal rather than oral estrogens be used in menopausal hormone therapy? A review. *Menopause Int* 2010;16:23-32.
34. Løkkegaard E, Andreasen AH, Jacobsen RK, Nielsen LH, Agger C, Lidegaard O. Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J* 2008;29:2660-2668.
35. Vongpatanasin W, Tuncel M, Wang Z, Arbique D, Mehrad B, Jialal I. Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. *J Am Coll Cardiol* 2003;41:1358-1363.
36. Hemelaar M, van der Mooren MJ, Rad M, Kluft C, Kenemans P. Effects of non-oral postmenopausal hormone therapy on markers of cardiovascular risk: a systematic review. *Fertil Steril* 2008;90:642-672.
37. Boschitsch E, Mayerhofer S, Magometschnigg D. Hypertension in women: the role of progesterone and aldosterone. *Climacteric* 2010;13:307-313.
38. Ashraf MS, Vongpatanasin W. Estrogen and hypertension. *Curr Hypertens Rep* 2006;8:368-376.
39. Rylance PB, Brincat M, Lafferty K, et al. Natural progesterone and antihypertensive action. *BMJ* 1985;290:13-14.
40. Hassager C, Riis BJ, Strøm V, Guyene TT, Christiansen C. The long-term effect of oral and percutaneous estradiol on plasma renin substrate and blood pressure. *Circulation* 1987;76:753-758.
41. Lee DY, Kim JY, Kim JH, et al. Effects of hormone therapy on ambulatory blood pressure in postmenopausal Korean women. *Climacteric* 2011;14:92-99.
42. Rosano M, Vitale C, Silvestri A, Fini M. Metabolic and vascular effect of progestins in post-menopausal women. Implications for cardioprotection. *Maturitas* 2003;46(suppl 1):S17-S29.
43. de Lauzon-Guillain B, Fournier A, Fabre A, et al. Menopausal hormone therapy and new-onset diabetes in the French Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort. *Diabetologia* 2009;52:2092-2100.
44. Chu MC, Cosper P, Nakhuda GS, Lobo RA. A comparison of oral and transdermal short-term estrogen therapy in postmenopausal women with metabolic syndrome. *Fertil Steril* 2006;86:1669-1675.
45. Rossouw J, Bray P, Liu J, et al. Estrogen receptor polymorphisms and the vascular effects of hormone therapy. *Arterioscler Thromb Vasc Biol* 2011;31:464-469.
46. Lobo RA, Clarkson TB. Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation. *Menopause* 2011;18:237-240.
47. 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;168:861-866.
48. Sare GM, Gray LJ, Bath PM. Association between hormone replacement therapy and subsequent arterial and venous vascular events: a meta-analysis. *Eur Heart J* 2008;29:2031-2041.
49. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. *BMJ* 2010;340:c2519.
50. Olié V, Plu-Bureau G, Conard J, Horellou MH, Canonico M, Scarabin PY. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. *Menopause* 2011;18:488-493.
51. Canonico M, Bouaziz E, Carcaillon L, et al. Synergism between oral estrogen therapy and cytochrome *P*450 3A5*1 allele on the risk of venous thromboembolism among postmenopausal women. *J Clin Endocrinol Metab* 2008;93:3082-3087.
52. Bagot CN, Marsh MS, Whitehead M, et al. The effect of estrone on thrombin generation may explain the different thrombotic risk between oral and transdermal hormone replacement therapy. *J Thromb Haemost* 2010;8:1736-1744.
53. Lobo RA. Risk of venous thromboembolism by route of administration of estrogen. *Menopause* 2011;18:469-470.
54. Scarabin PY, Alhene-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol* 1997;17:3071-3078.

55. Post MS, Christella M, Thomassen LG, et al. Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis: a randomized, placebo-controlled study in postmenopausal women. *Arterioscler Thromb Vasc Biol* 2003;23:1116-1121.
56. Oger E, Alhene-Gelas M, Lacut K, et al. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. *Arterioscler Thromb Vasc Biol* 2003;23:1671-1676.
57. Scarabin PY, Oger E, Plu-Bureau G, EStrogen and THromboEmbolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428-432.
58. Straczek C, Oger E, Yon de Jonage-Canonico MB, et al. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation* 2005;112:3495-3500.
59. Tremollieres F, Brincat M, Erel CT, et al. EMAS position statement: managing menopausal women with a personal or family history of VTE. *Maturitas* 2011;69:195-198.
60. Canonico M, Oger E, Conard J, et al. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost* 2006;4:1259-1265.
61. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER Study. *Circulation* 2007;115:840-845.
62. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;336:1227-1231.
63. Canonico M, Plu-Bureau G, Scarabin PY. Progestogens and venous thromboembolism among postmenopausal women using hormone therapy. *Maturitas* 2011;70:354-360.
64. Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *J Thromb Haemost* 2010;8:979-986.
65. Laliberté F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause* 2011;18:1052-1059.
66. Kahler KH, Nyirady J, Beresford E, et al. Does route of administration for estrogen hormone therapy and estradiol transdermal system dosage strength impact risk of venous thromboembolism. Paper presented at: NAMS 22nd Annual Meeting; September 23, 2011; Washington, DC.
67. Roach RE, Lijfering WM, Helmerhorst FM, et al. The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. *J Thromb Haemost* 2013;11:124-131.
68. Sweetland S, Beral V, Balkwill A, et al; The Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study [published online ahead of print September 10, 2012]. *J Thromb Haemost*. doi: 10.1111/j.1538-7836.2012.04919.x.
69. Canonico M, Alhenc-Gelas M, Plu-Bureau G, Olié V, Scarabin PY. Activated protein C resistance among postmenopausal women using transdermal estrogens: importance of progestogen. *Menopause* 2010;17:1122-1127.
70. American Cancer Society. Breast cancer facts & figures, 2009-2010. Available at: http://www.cancer.org/acs/groups/content/@nho/documents/document/f861009final90809pdf.pdf. Accessed November 28, 2012.
71. National Heart, Lung, and Blood Institute (NHLBI). Leading causes of death for American Women; 2007. Available at: http://www.nhlbi.nih.gov/educational/hearttruth/downloads/pdf/infographic-leadingcauses.pdf. Accessed November 28, 2012.
72. Society for Women's Health Research (SWHR). Women's fear of heart disease has almost doubled in three years, but breast cancer remains most feared disease: new survey shows what diseases women fear most; July 7, 2005. Available at: http://www.womenshealthresearch.org/site/News2?page=NewsArticle&id=5459&news_iv_ctrl=0&abbr=press_. Accessed November 28, 2012.
73. Bluming AZ, Tavris C. Hormone replacement therapy: real concerns and false alarms. *Cancer J* 2009;15:93-104.
74. Berman RS, Epstein RS, Lydick E. Risk factors associated with women's compliance with estrogen replacement therapy. *J Womens Health* 1997;6:219-226.
75. Pollycove R. Individualizing hormone supplementation/replacement therapy. San Francisco Medical Society Web site; April 2011. Available at: http://www.sfms.org/ForPatients/PhysicianFinder/PhysicianInfo/tabid/506/customercd/176079/Default.aspx. Accessed November 28, 2012.
76. Shapiro S, Farmer RD, Mueck AO, Seaman H, Stevenson JC. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies, 3: the Women's Health Initiative: unopposed estrogen. *J Fam Plann Reprod Health Care* 2011;37:225-230.
77. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat* 2008;107:103-111.
78. Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? *J Clin Oncol* 2009;27:5138-5143.
79. Stanczyk FZ. All steroids are not created equal. *Steroids* 2003;68:879-890.
80. Sitruk-Ware R. Pharmacological profile of progestogens. *Maturitas* 2008;61:151-157.
81. Wood CE, Register TC, Lees CJ, Chen H, Kimrey S, Cline JM. Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys. *Breast Cancer Res Treat* 2007;101:125-134.
82. Courtin A, Communal L, Vilasco M, et al. Glucocorticoid receptor activity discriminates between progesterone and medroxyprogesterone acetate effects in breast cells. *Breast Cancer Res Treat* 2012;131:49-63.
83. Harvey J, Scheurer C, Kawakami FT, Quebe-Fehling E, de Palacios PL, Ragavan VV. Hormone replacement therapy and breast density changes. *Climacteric* 2005;8:185-192.
84. Lippert C, Seeger H, Mueck AO. The effect of endogenous estradiol metabolites on the proliferation of human breast cancer cells. *Life Sci* 2003;72:877-883.
85. Lippert TH, Seeger H, Mueck AO. Estradiol metabolism during oral and transdermal estradiol replacement therapy in postmenopausal women. *Horm Metab Res* 1998;30:598-600.
86. Mueck AO, Seeger H, Lippert TH. Estradiol metabolism and malignant disease. *Maturitas* 2002;43:1-10.
87. Murkes D, Conner P, Leifland K, et al. Effects of percutaneous estradiol–oral progesterone versus oral conjugated equine estrogens–medroxyprogesterone acetate on breast cell proliferation and bcl-2 protein in healthy women. *Fertil Steril* 2011;95:1188-1191.
88. Santen RJ, Petroni GR. Relative versus attributable risk of breast cancer from estrogen replacement therapy. *J Clin Endocrinol Metab* 1999;84:1875-1881.
89. Fleiss JL, Levin B, Paik MC. *Statistical Methods for Rates and Proportions*, 3rd ed. New York: Wiley Interscience, 2003:125-129,151-154.
90. Hanley JA. A heuristic approach to the formulas for population attributable fraction. *J Epidemiol Community Health* 2001;55:508-514.
91. Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol* 2010;30:340-345.
92. Sturdee DW, Pines A, International Menopause Society Writing Group, et al. Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2011;14:302-320.
93. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95:s1-s66.
94. Tsai SA, Stefanick ML, Stafford RS. Trends in menopausal hormone therapy use of US office-based physicians, 2000-2009. *Menopause* 2011;18:385-392.
95. Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health* 2013;103:1583-1588.
96. Hodis HN. Is ET avoidance associated with early death in women with hysterectomy? Comment #2. In: *First to Know*. The North American Menopause Society. July 26, 2013. Available at: http://www.menopause.org/docs/default-source/professional/news0713special.pdf.
97. Utian WH. A decade post WHI, menopausal hormone therapy comes full circle—need for independent commission. *Climacteric* 2012;15:320-325.