The Timing Hypothesis and Hormone Replacement Therapy: A Paradigm Shift in the Primary Prevention of Coronary Heart Disease in Women. Part 2: Comparative Risks

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A major misperception concerning postmenopausal hormone replacement therapy (HRT) is that the associated risks are large in magnitude and unique to HRT, but over the past 10 years, sufficient data have accumulated so that the magnitude and perspective of risks associated with the primary coronary heart disease prevention therapies of statins, aspirin, and postmenopausal HRT have become more fully defined. Review of randomized controlled trials indicates that the risks of primary prevention therapies and other medications commonly used in women's health are of similar type and magnitude, with the majority of these risks categorized as rare to infrequent (<1 event per 100 treated women). Evidence-based data show that the risks of postmenopausal HRT are predominantly rare (<1 event per 1,000 treated women) and certainly no greater than other commonly used medications in women's health, including statins and aspirin. These risks, including breast cancer, stroke, and venous thromboembolism are common across medications and are rare, and even rarer when HRT is initiated in women younger than 60 or who are less than 10 years since menopause. In Part 1 of this series, the sex-specificity of statins and aspirin and timing of initiation of HRT as modifiers of efficacy in women were reviewed. Herein, the comparative risks of primary prevention therapies in women are discussed. **J Am Geriatr Soc 61:1011–1018, 2013.**

Key words: hormone therapy in women; statins; timing hypothesis; women and CHD prevention; meta-analyses; risks and benefits

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RISK OF THERAPIES USED FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE

Placing medications into clinical perspective relative to each other is the most common approach to understanding utility and reasonable acceptance of benefits and risks. In addition, understanding comparative risk on an absolute rather than relative scale permits realization and appreciation of true magnitude of risks, as well as the ability to compare the magnitude of risks of different medications using a commonly deployed standard[1] (Table 1).

There is a major misperception that postmenopausal hormone replacement therapy (HRT) is associated with risks that are large in magnitude and unique to HRT, but when contextualized with other medications that the Food and Drug Administration (FDA) has approved, it is apparent that the magnitude and type of risks associated with HRT are similar to those of other medications and therapies commonly used in clinical practice. As shown in Table 2, many of the risks associated with other medications and therapies commonly used in clinical practice exceed the rare category of risk and fall into the infrequent (uncommon) range of risk ($\geq$ 1/1,000 to <1/100), whereas the risks associated with HRT typically fall into the rare range of risk ($\geq$ 1/10,000 to <1/1,000). Regardless, rare to infrequent levels of risks are acceptable to the FDA, and the FDA considers all of the medications included in this review to be safe and effective. The purpose of this review is not to disparage any particular medication or therapy but to place the risks of HRT into proper perspective.

BREAST CANCER

No risk has been more misconstrued or misunderstood than that of breast cancer. Accumulating data show that statin therapy results in the same magnitude of breast cancer risk as that reported for daily, continuous combined conjugated equine estrogen plus medroxyprogesterone acetate (CEE + MPA) therapy, considered to be the HRT regimen with the greatest risk of breast cancer.[1]

In the Women's Health Initiative (WHI), breast cancer risk was originally reported to "almost reach nominal

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Table 1. Categorization of Adverse Drug Reactions: World Health Organization Council for International Organizations of Medical Sciences

Category	Frequency	
	N	%
Very common	≥1/10	≥10
Common (frequent)	≥1/100 to <1/10	≥1 to <10
Uncommon (infrequent)	≥1/1,000 to <1/100	≥0.1 to <1
Rare	≥1/10,000 to <1/1,000	≥0.01 to <0.1
Very rare	<1/10,000	<0.01

statistical significance" in the CEE + MPA arm (hazard ratio (HR) = 1.26, 95% confidence interval (CI) = 1.00–1.59) but was not significantly greater than placebo with the a priori statistic adjusted for multiple testing across time and outcome categories (HR = 1.26, 95% CI = 0.83–1.92).[2] This 26% increased risk accounted for 8 additional breast cancer cases per 10,000 women per year of CEE + MPA therapy, a rare event (<1 event per 1,000 treated women; Table 1). Adjustment of the original breast cancer data for breast cancer risk factors (i.e., age, body mass index, alcohol intake, physical activity, parity, family history, etc.) that were unequally distributed at baseline between treatment groups resulted in a nonsignificant nominal statistical difference in breast cancer incidence between CEE + MPA and placebo arms (HR = 1.20, 95% CI = 0.94–1.53).[3] Most importantly, women who were HRT naive (had never used HRT before randomization) when randomized to CEE + MPA therapy had no greater risk of breast cancer than those randomized to placebo (HR = 1.02, 95% CI = 0.77–1.36) over an average 5.6 years.[3] In other words, institution of CEE + MPA therapy in the typical postmenopausal woman who had never used HRT before beginning such therapy did not demonstrably increase the risk of breast cancer.[3]

The effect of CEE + MPA therapy on breast cancer in WHI was similar to the statistically nonsignificant 12 additional breast cancer cases per 10,000 women per year of CEE + MPA therapy reported in the Heart and Estrogen/progestin Replacement Study (HERS; HR = 1.30, 95% CI = 0.77–2.19).[4] Because blinding to CEE + MPA therapy is not completely possible because of vaginal bleeding, detection bias of outcomes is a possibility for WHI and HERS, as well as other similar trials. In addition, HERS, like WHI, was a study of older postmenopausal women more than 10 years beyond menopause and included only women with coronary heart disease (CHD), limiting generalizability.

Initial WHI CEE trial results showed a nonsignificant trend toward less breast cancer in the CEE arm than in the placebo arm (HR = 0.77, 95% CI = 0.59–1.01), accounting for eight fewer breast cancer cases per 10,000 women per year of CEE therapy (Figure 1).[5] Ductal carcinoma was 29% lower in the CEE arm than the placebo arm (HR = 0.71, 95% CI = 0.52–0.99).[6] Regardless of age at randomization into the WHI CEE trial, women had less breast cancer with CEE therapy, including those in the oldest age group (70–79) with the greatest expected risk.[6] Of women who took 80% or more of their study medication, those taking CEE were 33% less likely to develop breast cancer than those taking placebo (HR = 0.67, 95% CI = 0.47–0.97) after a mean randomized follow-up of 7.1 years.[6] The CEE-related trend in the reduction of breast cancer risk was confirmed in the WHI CEE follow-up study; over the entire follow-up period of 11 years (randomized and posttreatment phases), incidence of breast cancer in the CEE-treated group was 23% less than in the placebo group (HR = 0.77, 95% CI = 0.62–0.95).[7] Although based on a small sample, data from the Women's Estrogen for Stroke Trial (WEST) showed that oral daily 17β-estradiol had a null effect on breast cancer risk (HR = 1.00, 95% CI = 0.30–3.50).[8]

The Danish Osteoporosis Prevention Study (DOPS) confirmed these results, with randomization to oral 17β-estradiol daily plus sequential norethisterone acetate and unopposed 17β-estradiol 2 mg daily for 10 years reducing the risk of breast cancer 42% (HR = 0.58, 95% CI = 0.27–1.27), accounting for 14 fewer breast cancer cases per 10,000 women per year of HRT (Figure 1).[9] After 16 years of follow-up (10 years of randomized treatment and 6 years of postrandomization follow-up) in DOPS, the HRT effect on breast cancer reduction was attenuated but remained 10% (HR = 0.90, 95% CI = 0.52–1.57) lower in the women originally randomized to HRT than in those randomized to the control group.[9] Although these results should be interpreted with some caution because DOPS was an open-label trial with the control group receiving no trial intervention, detection bias would, if anything, have resulted in greater detection of breast cancers in HRT-treated women and a relative risk closer to the null value of 1. The DOPS sample size was small, with follow-up ascertainment of almost 100%.

The cumulative data show similar magnitudes of risk for new breast cancer diagnosis for statin therapy and daily continuous combined CEE + MPA[1] (Figure 1). Risk of breast cancer in women randomized to statin therapy ranges from 25% less to 12 times greater, accounting for an absolute risk of 10 fewer to 77 additional breast cancer cases per 10,000 women per year of statin therapy[1] (Figure 1). In three meta-analyses, statin therapy was associated with 9% to 33% greater breast cancer incidence than with placebo (relative risk (RR) = 1.33, 95% CI = 0.79–2.26, n = 11,001;[10] RR = 1.19, 95% CI = 0.81–1.73, n = 17,049;[11] RR = 1.09, 95% CI = 0.79–1.49, n = 21,575),[12] accounting for two to seven additional cases of breast cancer per 10,000 women per year of statin therapy.

The opposite effects reported from WHI trials on breast cancer risk for CEE + MPA (eight additional breast cancer cases per 10,000 women per year of CEE + MPA therapy) versus CEE (eight fewer breast cancer cases per 10,000 women per year of CEE therapy) has led to the assumption that MPA in continuous combination with CEE confers the negative effects on breast cancer not observed with CEE alone, but differential unblinding that occurred in WHI is an equally plausible explanation. The association between CEE + MPA and breast cancer risk reported from WHI may have erroneously arisen not only through the confounding bias of differing distribution of breast cancer risk factors between treatment groups at

Table 2. Relative and Absolute Risks of Commonly Used Medications and Supplements

Therapy	Event	References	Risk Ratio (95% Confidence Interval)	Additional Cases/10,000 Persons per Year
Mortality				
Fenofibrate	Total mortality	Lancet 2005;366:1849–1861	1.11 (0.95–1.29)	13
Lovastatin	Total mortality	J Women's Health Gen Based Med 2001;10:971–981	Not reported	15
Atorvastatin	Total mortality	N Engl J Med 2006;355:549–559	1.00 (0.82–1.21)	4
Beta-carotene	Total mortality	N Engl J Med 1996;334:1150–1155	1.17 (1.03–1.33)	25
Calcium supplements	Total mortality	BMJ 2008;336:262–266	1.18 (0.73–1.92)	15
Intensive DM control	Total mortality	N Engl J Med 2008;358:2545–2559	1.22 (1.01–1.46)	27
Intensive DM control	Total mortality	N Engl J Med 2009;360:129–139	1.07 (0.81–1.42)	15
Naproxen	Total mortality	PLoS Clin Trials 2006;1:e33	1.37 (0.60–3.10)	14
Pravastatin	Nonvascular mortality	Lancet 2002;360:1623–1630	1.57 (0.80–3.08)	9
Aspirin	Sudden death	N Engl J Med 1989;321:129–135	1.96 (0.91–4.22)	2
Fenofibrate	CVD mortality	Lancet 2005;366:1849–1861	1.11 (0.87–1.41)	5
Zoledronate	CVD mortality	N Engl J Med 2007;356:1809–1822	Not reported	5
Intensive DM control	CVD mortality	N Engl J Med 2008;358:2545–2559	1.35 (1.04–1.76)	23
Naproxen	CVD mortality	PLoS Clin Trials 2006;1:e33	1.48 (0.30–7.32)	5
Pravastatin	Stroke mortality	Lancet 2002;360:1623–1630	1.57 (0.80–3.08)	9
Zoledronate	Stroke mortality	N Engl J Med 2007;356:1809–1822	Not reported	7
Fenofibrate	Cancer mortality	Lancet 2005;366:1849–1861	Not reported	9
Atorvastatin	Cancer mortality	N Engl J Med 2006;355:549–559	1.05 (0.72–1.53)	3
Pravastatin	Cancer mortality	Lancet 2002;360:1623–1630	1.28 (0.97–1.68)	26
Naproxen	Cancer mortality	PLoS Clin Trials 2006;1:e33	1.86 (0.50–6.93)	11
Cancer				
Pravastatin	New cancer diagnosis	Lancet 2002;360:1623–1630	1.25 (1.04–1.51)	51
Lovastatin	New cancer diagnosis	J Women's Health Gen Based Med 2001;10:971–981	Not reported	7
Pravastatin	Breast cancer diagnosis	Lancet 2002;360:1623–1630	1.65 (0.78–3.49)	15
Lovastatin	Breast cancer	J Women's Health Gen Based Med 2001;10:971–981	Not reported	15
Beta-carotene	Lung cancer	N Engl J Med 1996;334:1150–1155	1.28 (1.04–1.57)	13
Stroke and venous thromboembolism				
Pravastatin	Fatal or nonfatal stroke	Lancet 2002;360:1623–1630	1.03 (0.81–1.31)	5
Intensive DM control	Nonfatal stroke	N Engl J Med 2008;358:2545–2559	1.06 (0.75–1.50)	2
Atorvastatin	Hemorrhagic stroke	N Engl J Med 2006;355:549–559	1.66 (1.08–2.55)	19
Simvastatin	Hemorrhagic stroke	Lancet 2004;363:757–767	1.86 (not reported)	2
Aspirin	Hemorrhagic stroke	N Engl J Med 2005;352:1293–1304	1.24 (0.82–1.87)	1
Rosiglitazone	Stroke	Lancet 2006;368:1096–1105	1.39 (0.44–4.40)	3
Calcium supplements	Stroke	BMJ 2008;336:262–266	1.45 (0.88–2.49)	36
Naproxen	Stroke	PLoS Clin Trials 2006;1:e33	2.13 (0.81–5.60)	25
Fenofibrate	Deep vein thrombosis	Lancet 2005;366:1849–1861	Not reported	7
Fenofibrate	Pulmonary embolus	Lancet 2005;366:1849–1861	Not reported	9
CHD				
Calcium supplements	CHD (MI, stroke, sudden death)	BMJ 2008;336:262–266	1.43 (1.01–2.04)	70
Rosiglitazone	CVD events	Lancet 2006;368:1096–1105	1.37 (0.97–1.94)	25
Rosiglitazone	MI	Lancet 2006;368:1096–1105	1.66 (0.73–3.80)	8
Rosiglitazone	MI	Lancet 2009;373:2125–2135	1.14 (0.80–1.63)	6
Calcium supplements	MI	BMJ 2008;336:262–266	1.67 (0.98–2.87)	45
Naproxen	MI	PLoS Clin Trials 2006;1:e33	1.49 (0.69–3.22)	21
Alendronate	Atrial fibrillation	Arch Intern Med 2008;168:826–831	1.86 (1.09–3.15)	Not reported
Zolendronate	Serious atrial fibrillation	N Engl J Med 2007;356:1809–1822	~2.5 ($P < .001$)	26
Heart failure				
Rosiglitazone	Heart failure	Lancet 2009;373:2125–2135	2.10 (1.35–3.27)	26
Pioglitazone	Heart failure	Lancet 2005;366:1279–1289	Not reported	77
Intensive DM control	Fatal or nonfatal CHF	N Engl J Med 2008;358:2545–2559	1.18 (0.93–1.49)	15
Pioglitazone	Fatal heart failure	Lancet 2005;366:1279–1289	Not reported	4
Bone fracture				
Rosiglitazone	Bone fracture	Lancet 2009;373:2125–2135	1.82 (1.37–2.41)	94
Pioglitazone	Bone fracture	Can Med Assoc J 2009;180:32–39	2.04 (1.22–3.41)	88
Proton pump inhibitors	Hip fracture	BMJ 2012;344:e372	1.35 (1.13–1.62)	5

(Continued)

Table 2 (Contd.)

Therapy	Event	References	Risk Ratio (95% Confidence Interval)	Additional Cases/10,000 Persons per Year
Bisphosphonates	Atypical spiral fracture of the femoral shaft	N Engl J Med 2011;364;1728–1737	47.3 (25.6–87.3)	5
GI bleeding				
Aspirin	GI bleeding requiring blood transfusion	N Engl J Med 2005;352:1293–1304	1.40 (1.07–1.83)	2
Aspirin	GI bleeding	N Engl J Med 2005;352:1293–1304	1.22 (1.10–1.34)	8
Dementia				
Benzodiazepines	Dementia	BMJ 2012;345;e6231	1.62 (1.08–2.43)	57

DM = diabetes mellitus; CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; CHF = congestive heart failure; GI = gastrointestinal.

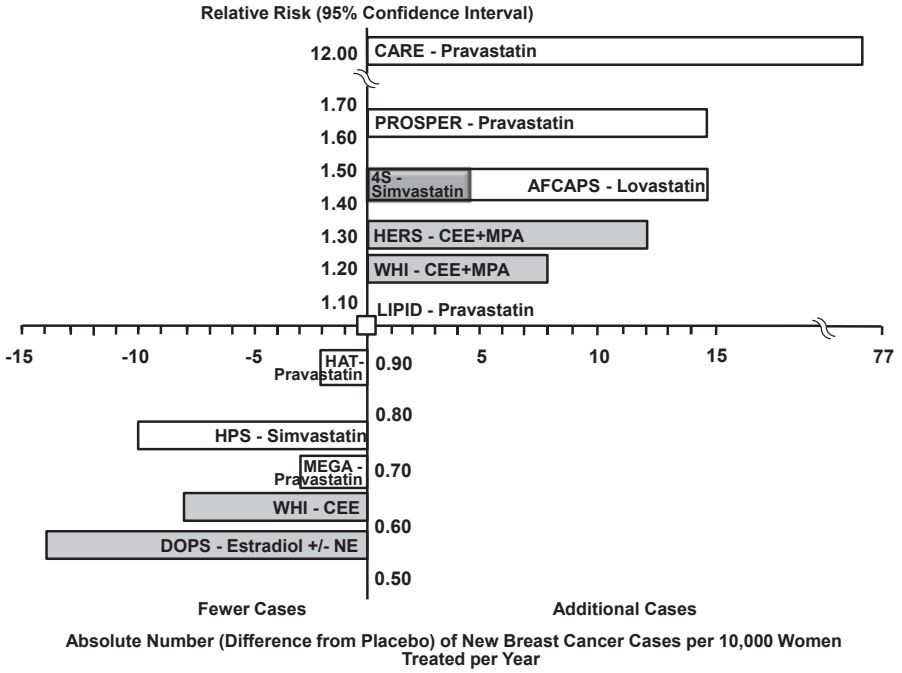

Figure 1. Relative and absolute breast cancer risk (difference from placebo) in randomized controlled trials of statin and hormone replacement therapy. The absolute risk of breast cancer ranges from 10 fewer to 77 additional new breast cancer cases per 10,000 women per year of statin therapy, comparable with rates for conjugated equine estrogen (CEE; eight fewer new breast cancer cases per 10,000 women per year of CEE therapy) and for CEE plus medroxyprogesterone acetate (MPA; eight additional new breast cancer cases per 10,000 women per year of CEE + MPA therapy) in the Women's Health Initiative (WHI) trials and similar to the Danish Osteoporosis Prevention Study (DOPS) after randomization for 10 years (14 fewer new breast cancer cases per 10,000 women per year of oral 17β-estradiol with and without sequential norethisterone (NE)). Boxes represent absolute number of breast cancer cases. CARE = Cholesterol and Recurring Events; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; 4S = Scandinavian Simvastatin Survival Study; AFCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; HAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; HPS = Heart Protection Study; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese. Citations to the studies in this figure can be found in reference (1).

baseline[3] (see above), but also through a detection bias caused by greater unblinding of CEE + MPA than placebo treatment.[13,14] Predominantly because of vaginal bleeding, at least 44.4% of CEE + MPA recipients and 6.8% of placebo recipients were unblinded to treatment assignment,[2,13,14] and over time, the WHI CEE + MPA trial took on observational study characteristics as subjects became increasingly aware of their treatment status. This large difference in awareness of treatment status between HRT and placebo (a 6.5-times relative difference and a 37.6% absolute difference) provides the basis for detection bias. To the contrary, all women in the WHI CEE trial had hysterectomies, and only 1.9% of CEE recipients and 1.5% of placebo recipients were unblinded to their treatment assignment[5,13,14] indicating no detection bias and that methods and findings in the WHI CEE trial are more valid than those from the WHI CEE + MPA trial.[13,14]

STROKE

Although WEST has been the only randomized controlled trial (RCT) of HRT designed with stroke as the primary trial outcome,[8] HERS and WHI also provide information concerning stroke as an additional trial outcome. In WEST, 664 postmenopausal women who were ischemic stroke survivors and on average 71 years old and approximately 20 years postmenopausal at randomization, oral 17β-estradiol 1 mg/d had a null effect on the primary outcome of nonfatal stroke or death relative to placebo (RR = 1.1, 95% CI = 0.8–1.4).[8]

In HERS, daily continuous combined CEE + MPA was associated with a nonsignificant increase in primary stroke risk (HR = 1.23, 95% CI = 0.89–1.70) in postmenopausal women with established CHD who were on average 67 years old and 18 years postmenopausal when randomized to HRT.[15] In the WHI CEE + MPA (HR = 1.31; nominal 95% CI = 1.02–1.68; multiplicity-adjusted 95% CI = 0.93–1.84)[16,17] and WHI CEE (HR = 1.33; nominal 95% CI = 1.05–1.68; multiplicity-adjusted 95% CI = 0.97–1.99)[5,16] trials, there were eight and 11 additional strokes per 10,000 women per year of CEE + MPA and CEE therapy, respectively, than with placebo. Adjustment for multiple testing across time and across outcome categories (multiplicity-adjusted) included the null value of 1, was the a priori defined outcome of stroke in WHI. Women randomized to the WHI trials were on average 64 years old and more than 12 years postmenopausal. In a subset of 1,403 WHI participants aged 65 to 79 who underwent magnetic resonance brain imaging on average 8 years after randomization to CEE + MPA or CEE, there was no significant difference in ischemic lesion volume between those who received CEE + MPA or CEE and those who received placebo.[18] As such, this neuroradiological substudy provides no evidence within or between WHI trials according to treatment assignment that HRT increases ischemic lesion volume, although ischemic lesion volume was associated with several vascular risk factors, including age, smoking, history of cardiovascular disease, and hypertension, indicating internal validity of the neuroradiological outcomes and stroke risk factors in WHI.[18]

The association between CEE + MPA and CEE and stroke is predominantly reported in older women (average age 64) more than 10 years since menopause when initiating these therapies. Stroke is rare in women who initiate HRT when younger than 60:[16] five additional strokes per 10,000 women per year of CEE + MPA therapy (HR = 1.41, 95% CI = 0.75–2.65) and two fewer strokes per 10,000 women per year of CEE therapy (HR = 0.89, 95% CI = 0.47–1.69) relative to placebo than in WHI.[16] With the WHI CEE + MPA and WHI CEE trials combined, there were two additional strokes per 10,000 women per year of CEE + MPA and CEE therapy when initiated in women younger than 60 (HR = 1.13, 95% CI = 0.73–1.76). DOPS is consistent with these and the WEST findings, with oral 17β-estradiol plus sequential norethisterone acetate and unopposed 17β-estradiol 2 mg/d initiated on average 7 months from menopause resulting in 23% (HR = 0.77, 95% CI = 0.35–1.70) lower risk of stroke than in the control group (6 fewer strokes per 10,000 women per year of HRT) after 10 years of randomization and 11% (HR = 0.89, 95% CI = 0.48–1.65) lower risk after 16 years of total follow-up (10 years of randomized treatment and 6 years of postrandomization follow-up).[9]

VENOUS THROMBOEMBOLISM

In the WHI CEE + MPA trial, CEE + MPA therapy was associated with significantly greater venous thromboembolism (VTE) risk (HR = 2.11, nominal 95% CI = 1.58–2.82; multiplicity-adjusted 95% CI = 1.26–3.55),[2,19] accounting for a slightly greater absolute risk (18 additional VTE events per 10,000 women per year of CEE + MPA therapy).[2,19] Absolute VTE risk was lowest for women younger than 60 when randomized (11 additional VTE events per 10,000 women per year of CEE + MPA therapy).[19] Overall, there were seven additional VTE events per 10,000 women per year of CEE therapy in the WHI CEE trial (HR = 1.33; nominal 95% CI = 0.99–1.79; multiplicity-adjusted 95% CI = 0.86–2.08).[5,20] Absolute VTE risk was lowest for women younger than 60 when randomized (4 additional VTE events per 10,000 women per year of CEE therapy).[20] In WEST, there was a 20% nonsignificant decrease in VTE events (HR = 0.80, 95% CI = 0.20–3.40), accounting for 12 fewer VTE events per 10,000 women per year of 17β-estradiol therapy.[8]

In DOPS, after 10 years of randomized treatment, three women had confirmed deep vein thrombosis (DVT; two in the HRT group, one in the control group; HR = 2.01, 95% CI = 0.18–22.16). One woman in the control group was hospitalized with pulmonary embolism (PE). After a follow-up of 16 years, nine women had confirmed DVT (four in the HRT group, five in the control group; HR = 0.80, 95% CI = 0.22–2.99). Four women were hospitalized with PE (one in the HRT group, three in the control group; HR = 0.33, 95% CI = 0.04–3.21).[9]

COMPARING RISKS OF HRT WITH RISKS OF OTHER MEDICATIONS USED IN WOMEN'S HEALTH

Medications commonly used in women's health are associated with a similar magnitude of risk for stroke and VTE and possess other risks equal to or greater than those of HRT. In particular, in postmenopausal women, the absolute stroke risk is higher with calcium supplementation (36 additional strokes per 10,000 women per year of calcium supplementation) than with HRT (Table 2). Although aspirin reduces ischemic stroke by 24% in women without preexisting CVD, risk of hemorrhagic stroke is 24% greater with aspirin; risk of hemorrhagic stroke is 18% lower with CEE + MPA therapy (HR = 0.82, 95% CI = 0.43–1.56)[17] and 36% lower with CEE therapy (HR = 0.64, 95% CI = 0.35–1.18)[21] than with placebo. RCTs for secondary prevention of CHD have shown greater risk of hemorrhagic stroke with statin therapy (Table 2). VTE events have also been reported with medications such as fenofibrate of the same magnitude as HRT (Table 2). Certain notable risks associated with other medications but not reported with HRT include total mortality and mortality from cardiovascular disease, stroke, and cancer (Table 2).

Although HRT is the only therapy shown in large RCTs (specifically WHI) to reduce bone fractures in a general population of women not preselected for high risk of bone fracture (e.g., low T-score) or with prior fracture,[2,5] bisphosphonates have become standard osteoporotic therapy. However, bisphosphonates significantly increase risk of atrial fibrillation (Table 2) to a magnitude (26 additional serious atrial fibrillation events per 10,000 women per year of bisphosphonate therapy) greater than any risk associated with HRT and cause atypical spiral fractures of the femoral shaft, especially with increasing duration of bisphosphonate use (10 times greater risk than control within the first 2 years of use and 50 times greater risk thereafter)[22] (Table 2). Other medications increase bone fracture risk in women, including thiazolidinediones and proton pump inhibitors, accounting for five to 94 additional bone fractures per 10,000 women per year of therapy (Table 2). Certain medication-related risks appear to be greater in women than men, such as bone fracture risk with thiazolidinediones and new-onset diabetes mellitus with statins.[23]

NEW-ONSET DIABETES MELLITUS AND PRIMARY PREVENTION THERAPIES

An important consideration before initiation of primary prevention therapy for CHD is the risk of new-onset diabetes mellitus. In WHI, new-onset diabetes mellitus was 21% less likely in the CEE + MPA-treated group than with placebo (HR = 0.79, 95% CI = 0.67–0.93), accounting for 15 fewer cases of new-onset diabetes mellitus per 10,000 women per year of CEE + MPA therapy.[24] In HERS, new-onset diabetes mellitus was 35% lower in the CEE + MPA treated group than with placebo (HR = 0.65, 95% CI = 0.48–0.89) accounting for 81 fewer cases of new-onset diabetes mellitus per 10,000 women per year of CEE + MPA therapy.[25] In WHI, new-onset diabetes mellitus was 12% lower in the CEE treated group than with placebo (HR = 0.88, 95% CI = 0.77–1.01), accounting for 14 fewer cases of new-onset diabetes mellitus per 10,000 women per year of CEE therapy.[26] In a meta-analysis of 107 RCTs, incident diabetes mellitus was 30% lower with HRT than with placebo (HR = 0.70, 95% CI = 0.6–0.9).[27]

In contrast, statin therapy carries an FDA warning for risk of new-onset diabetes mellitus.[28] In a meta-analysis of six RCTs of 57,593 women and men, statin therapy was associated with a significantly greater risk of incident diabetes mellitus than placebo (HR = 1.13, 95% CI = 1.03–1.23), accounting for eight additional cases of new-onset diabetes mellitus per 10,000 individuals per year of statin therapy.[29] In another meta-analysis of 13 RCTs of 91,140 women and men, statin therapy was associated with a significantly greater risk of incident diabetes mellitus than placebo (HR = 1.09, 95% CI = 1.02–1.17), accounting for 10 additional cases of new-onset diabetes mellitus per 10,000 individuals per year of statin therapy.[30] In a meta-analysis of five RCTs with 32,752 women and men, intensive-dose statin therapy was associated with a significantly greater risk of incident diabetes mellitus than moderate-dose statin therapy (HR = 1.12, 95% CI = 1.04–1.22), accounting for 20 additional cases of new-onset diabetes mellitus per 10,000 individuals per year of intensive-dose statin therapy.[31]

Women are particularly susceptible to statin-induced new-onset diabetes mellitus.[23] In Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), incident diabetes mellitus was significantly greater in women in the rosuvastatin arm than in those taking placebo (HR = 1.49, 95% CI = 1.11–2.01) and nonsignificantly greater in men (HR = 1.14, 95% CI = 0.91–1.43).[23] In women, 50 additional incident diabetes mellitus cases per 10,000 women per year of rosuvastatin treatment were reported from JUPITER, whereas in men 16 additional incident diabetes mellitus cases per 10,000 men per year of rosuvastatin treatment were reported.[23] In the largest study to date, with 1,004,446 women-years of follow-up, the WHI has verified the risk of new-onset diabetes mellitus in postmenopausal women who use statins in a nonrandomized setting. WHI showed in a cohort of 153,840 postmenopausal women a 48% (HR = 1.48, 95% CI = 1.38–1.59) greater risk of incident diabetes mellitus, accounting for 117 more cases of new-onset diabetes mellitus per 10,000 women per year of statin therapy than in women who did not use statins.[32]

CONCLUSION

Evidence-based data from randomized trials are reassuring in that risks associated with HRT are rare (<1 event per 1,000 treated women) and even rarer in women who initiate HRT when they are younger than 60 or in whom it has been less than 10 years since menopause. Randomized trials also show that HRT risks of most concern—breast cancer, stroke, and VTE—are not unique to HRT and are of similar magnitude to risks of other medications that women commonly use (Table 2).

Although breast cancer risk may or may not be greater with HRT delivered as CEE + MPA, the WHI Estrogen plus Progestin trial did not establish that it is, although it established that, if breast cancer is associated with CEE + MPA, it is rare and similar to the risk associated with statin use. Nevertheless, breast cancer risk is clearly lower with CEE therapy, and in women who adhere to CEE therapy, the risk of breast cancer is significantly lower (30%), which is demonstrable for up to 11 years of follow-up. Randomized trials show no breast cancer risk with 17β-estradiol at any age, and in DOPS, young postmenopausal women who initiated oral 17β-estradiol with and without progestin in close proximity to menopause had a lower risk of breast cancer over 10 years of randomized treatment and for up to 16 years of total follow-up.

Consistent with the accumulated data that predominantly show a lack of association between HRT and stroke, the additional absolute risk associated with HRT is rare when considered across all ages and even rarer when initiated in women younger than 60 or who are less than 10 years since menopause. The risk in younger postmenopausal women who initiate HRT in close proximity to menopause approximates two fewer stroke per 1,000 women over 10 years of CEE therapy and five additional strokes per 1,000 women over 10 years of CEE + MPA therapy. Randomized trials show no stroke risk with oral 17β-estradiol therapy over all ages, and young postmeno-

pausal women who initiate oral 17β-estradiol with and without progestin have a lower risk of stroke for up to 16 years. DOPS shows six fewer strokes per 1,000 women over 10 years of HRT. VTE with CEE + MPA therapy appears to be the only consistent statistically significant risk, but it is rare in women who initiate CEE + MPA when younger than 60 or who are less than 10 years since menopause. Randomized trials show no VTE risk with oral 17β-estradiol therapy with or without progestin with up to 16 years of follow-up.

The risks and benefits of HRT vary according to dosage, regimen, and timing of initiation. As such, broad conclusions concerning HRT risks are not possible, and attempts to generalize risk from the WHI regimen of daily continuous combined CEE + MPA to all HRT have resulted in misleading and inaccurate information concerning HRT. Although the risks and benefits of HRT continue to be debated, perhaps one of the most unfortunate consequences of casting HRT in a negative light has been the overshadowing of the fact that published studies consistently show that HRT reduces total mortality by approximately 30% when it is initiated in young postmenopausal women and continued over the long term (see Part 1).[33] This consistent beneficial effect of HRT on total mortality contrasts with the many medications and therapies used in clinical medicine that increase mortality and are considered more, some of which have been shown to statistically significantly increase the risk of mortality, such as intensive control of diabetes mellitus (Table 2).

In conclusion, HRT risks are rare and are no greater than those of other medications or primary prevention therapies used in women, indicating the safety of HRT. As discussed in Part 1, HRT effectively reduces CHD and total mortality (statins and aspirin do not) when initiated in women younger than 60 or who are less than 10 years since menopause and can be safely used to do so.[33]

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