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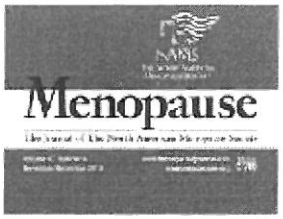
Methods and Baseline Cardiovascular Data From the Early Versus Late Intervention Trial With Estradiol Testing the Menopausal Hormone Timing Hypothesis



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Abstract and Introduction

Abstract

Objective. This study aims to present methods and baseline data from the Early versus Late Intervention Trial with Estradiol (ELITE), the only clinical trial designed to specifically test the timing hypothesis of postmenopausal hormone therapy (HT). The timing hypothesis posits that HT effects depend on the temporal initiation of HT relative to time since menopause.

Methods. ELITE is a randomized, double-blind, placebo-controlled trial with a 2 × 2 factorial design. Six hundred forty-three healthy postmenopausal women without cardiovascular disease were randomized to oral estradiol or placebo for up to 6 to 7 years according to time since menopause (<6 or ≥10 y). Carotid artery intima-media thickness (CIMT) and cardiac computed tomography were conducted to determine HT effects on subclinical atherosclerosis across menopause strata.

Results. Participants in the early and late postmenopausal strata were well-separated by mean age (55.4 vs 65.4 y) and median time since menopause (3.5 vs 14.3 y). Expected risk factors (age, blood pressure, and body mass index) were associated with CIMT at baseline in both strata. In the early postmenopausal group, but not in the late postmenopausal group, we observed significant associations between CIMT and factors that may play a role in the responsiveness of atherosclerosis progression according to timing of HT initiation. These include low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, sex hormoneYbinding globulin, and serum total estradiol.

Conclusions. The ELITE randomized controlled trial is timely and unique. Baseline data indicate that ELITE is well-positioned to test the HT timing hypothesis in relation to atherosclerosis progression and coronary artery disease.

Introduction

The "timing," "critical window," or "window of opportunity" hypothesis of hormone therapy (HT) was proposed to explain the difference in outcomes between randomized clinical event trials and observational studies of coronary heart disease (CHD),[1,2] cognition, and dementia.[3,4] The timing hypothesis posits that HT benefits and risks depend on the temporal initiation of HT relative to time since menopause, age, or both, which are in turn related to the health of the underlying tissue (ie, healthy vascular endothelium and extent of atherosclerosis burden) or to some other factors such as age-related reduction in estrogen receptors or receptor downregulation.[5,6] The divergent results between the atherosclerosis progression sister trials Estrogeninthe Prevention of Atherosclerosis Trial (EPAT)[5] and Women's Estrogen Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART)[6] provided early clinical trial support for this hypothesis. Although EPAT demonstrated a reduction of subclinical atherosclerosis progression with HT in postmenopausal women without demonstrable atherosclerosis, WELL-HART demonstrated a null effect on postmenopausal women with documented coronary artery atherosclerosis.[5,6] Experimental animal studies[7-9] have replicated the divergent effects of HT on atherosclerosis, as shown in EPAT and WELL-HART, with findings later complemented by clinical outcome trials such as the Women's Health Initiative (WHI).[10] With the completion of EPAT and WELL-HART, a new randomized controlled trial—entitled the Early versus Late Intervention Trial with Estradiol (ELITE)— was proposed to the National Institutes of Health in early 2002 to test the timing hypothesis.

Data supporting the timing hypothesis have grown considerably during the past decade since the initiation of ELITE.[1] ELITE remains unique and timely as it is the only randomized controlled trial specifically designed to test the timing hypothesis of HT in relation to atherosclerosis progression and cognitive changes in postmenopausal women. The primary ELITE hypothesis is that postmenopausal HT reduces the progression of subclinical atherosclerosis, coronary artery disease (CAD), and cognitive changes in postmenopausal women without clinical evidence of cardiovascular disease (CVD) when initiated soon after menopause (<6 y), relative to initiation of HT when distant from menopause (≥10 y). Subclinical atherosclerosis baseline data are detailed in this publication, whereas cognitive baseline data are detailed elsewhere.[11]

Methods

Design

ELITE is a single-center, randomized, double-blind, placebocontrolled, noninvasive serial arterial imaging, prospective trial with a 2 × 2 factorial design (clinical trial registration: NCT00114517). Healthy postmenopausal women without clinical evidence of CVD were randomized to active HT or to placebo according to time since menopause (<6 y [early postmenopause] or ≥10 y [late postmenopause]). Recruitment was initially based on a 5-year trial (3-y recruitment period and 2-5 y of randomized treatment). In the fifth year of randomized follow-up, the trial was extended for an additional 2.5 years of randomized intervention. As part of the ELITE extension, a third cognitive assessment was added,[11] and measurements of subclinical coronary artery atherosclerosis are obtained as participants complete the trial.

Treatment

Women with intact uterus were randomized to oral micronized 17β-estradiol 1 mg/day with 4% vaginal micronized progesterone gel 45 mg/day for 10 days each month or to double-matched placebos. Women without intact uterus were randomized to oral micronized 17β-estradiol 1 mg/day alone or to placebo.

Eligibility Criteria

Eligible participants were postmenopausal women without clinical evidence of CVD, with a serum estradiol level lower than 25 pg/mL, and with cessation of regular menses for a minimum of 6 months who had been postmenopausal for less than 6 years or for 10 years or more at the time of randomization. Exclusion criteria included the following: women in whom time since menopause could not be determined; fasting plasma triglycerides (TG) level higher than 500 mg/dL; diabetes mellitus or fasting serum blood glucose level higher than 140 mg/dL; serum creatinine level higher than 2.0 mg/dL; uncontrolled hypertension (systolic blood pressure/diastolic blood pressure >160/110 mm Hg); untreated thyroid disease; life-threatening disease with prognosis of less than 5 years; history of deep vein thrombosis, pulmonary embolism, or breast cancer; and current postmenopausal HT (within 1 mo of screening).

Randomization

Participants were randomized to active HT or to placebo in strata defined by time since menopause (<6 or ≥10 y). Additional randomization stratification factors included hysterectomy (yes or no) and baseline carotid artery intima-media thickness (CIMT; <0.75 or ≥0.75 mm; Figure 1). Trial eligibility was assessed at the screening and baseline visits and confirmed at the data coordinating center. Assignment to HT or to placebo (in a 1:1 ratio) was performed using stratified blocked randomization not identified to study personnel. Randomization lists for each of the eight strata were prepared by the trial statistician before trial initiation; blinded study product was prepared based on the stratified randomization lists. Upon determination of trial eligibility and stratum for a given participant, clinic staff pulled the next study product in sequence from the appropriate stratum and recorded the product identification number. The fidelity of the randomization process was monitored at the data coordinating center. Participants, investigators, staff, imaging specialists, and data monitors are masked to treatment assignment.

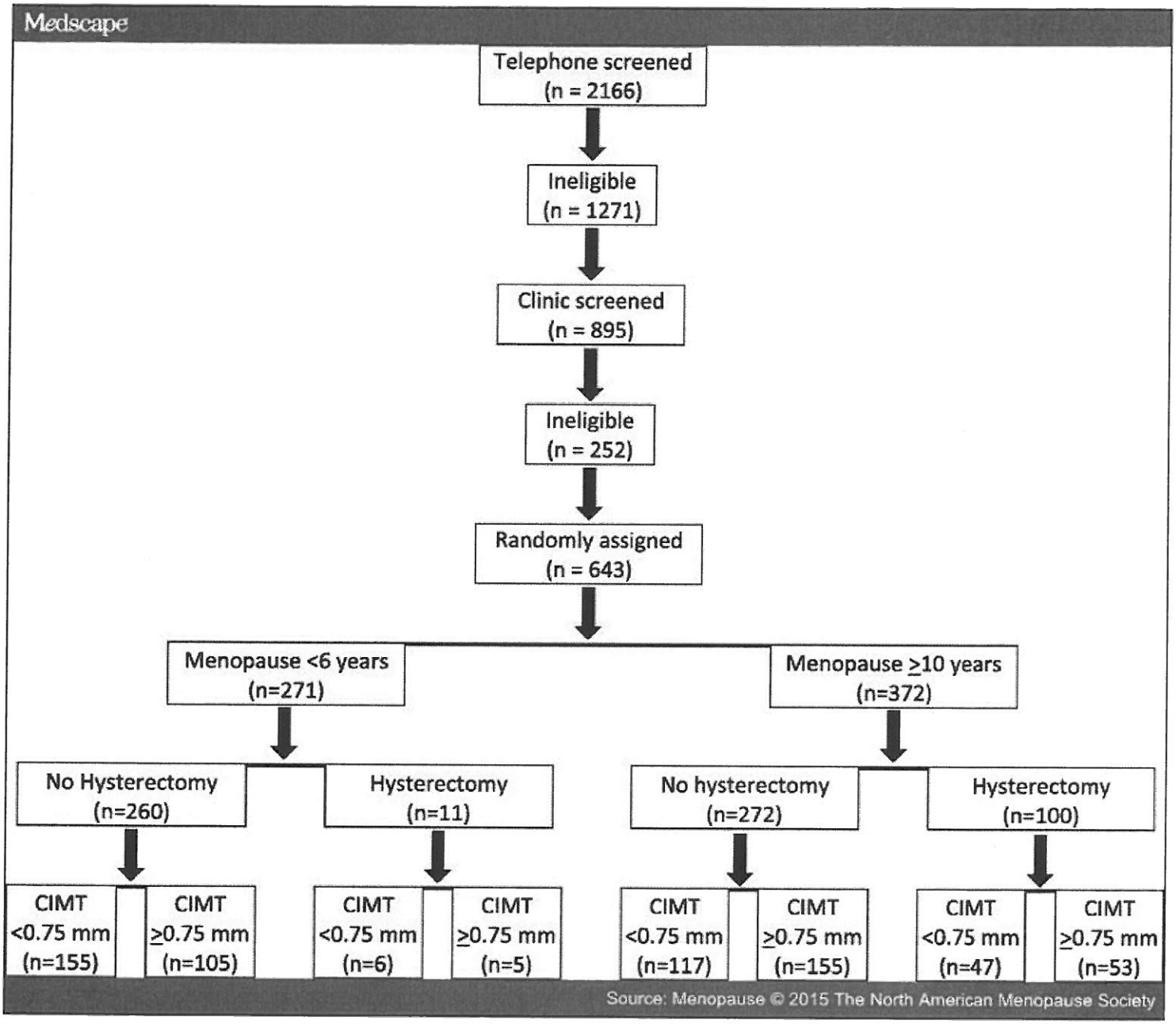

Figure 1.

Consolidated Standards of Reporting Trials flowchart for the Early versus Late Intervention Trial with Estradiol summarizing the recruitment and randomization process. CIMT, carotid artery intima-media thickness.

Follow-up

After randomization, participant evaluations are conducted in a specialized research clinic every month for the first 6 months of the trial and then every other month until trial completion. All baseline evaluations were conducted before randomization. Every 6 months, fasting blood is obtained for the following analyses: plasma estradiol is quantified by radioimmunoassay with preceding organic solvent extract and Celite column partition chromatography steps[12]; sex hormone-binding globulin (SHBG) is measured on the Immunlite analyzer (Siemens Healthcare Diagnostics, Deerfield, IL); plasma lipids and lipoproteins (total cholesterol [TC], total TG, low-density lipoprotein cholesterol [LDL-C], LDL-TG, very-low-density lipoprotein cholesterol [VLDL-C], VLDL-TG, high-density lipoprotein cholesterol [HDL-C], and HDL-TG) are measured by preparative ultracentrifugation and enzymatic assays standardized to the Centers for Disease Control using Lipid Research Clinic protocol[5]; and plasma hemoglobin A1c is determined by high-pressure liquid chromatography-ion exchange chromatography (Diabetes Control and Complications Trial-approved method).[13] Complete blood count and chemistry panel are completed yearly by Quest Diagnostics.

Blood pressure, pulse rate, and weight are determined at baseline and then at each visit. Waist circumference and hip circumference are obtained every 6 months, and height was obtained at baseline. A 12-lead electrocardiogram is obtained yearly. Questionnaires covering medical history, angina, claudication, physical activity, smoking, and alcohol use are administered every 6 months. Study product compliance, clinical events (MedDRA-coded), and use of nonstudy medications and nutritional supplements are ascertained at every clinic visit. Participants complete 3-day dietary booklets (Nutrition Scientific) before the baseline visit and before each subsequent clinic visit.

Reproductive history was obtained at baseline. The Center for Epidemiologic Studies Depression scale and the Women's Health Questionnaire[14] covering physical and emotional health were administered at baseline and then at every 6 months. Participants complete hot flash, vaginal bleeding and cramping, and breast pain diaries that are collected at baseline and at each clinic visit. Mammography, gynecological examinations (including Papanicolaou test), transvaginal uterine ultrasound, and endometrial biopsy (if indicated) are performed at baseline, annually, and as indicated.

Primary Endpoint

All women who met the trial inclusion criteria underwent two baseline B-mode carotid artery ultrasound examinations to acquire standardized images for CIMT measurements. The first CIMT was assessed at the screening visit and was used to determine randomization stratum. The second CIMT was conducted at the baseline visit before randomization among women who met the final trial inclusion criteria. The time interval between the first CIMT and the second CIMT was 2 to 4 weeks. The primary trial endpoint is the rate of change in the right distal common carotid artery far wall intima-media thickness on computer imageYprocessed B-mode ultrasonograms determined at the two baseline examinations and serial examinations completed every 6 months during trial follow-up.[5] Highresolution B-mode ultrasound imaging and measurement of far wall CIMT are conducted using standardized procedures and technology specifically developed for longitudinal measurements of atherosclerosis change (patents 2005, 2006, and 2011). Details of ultrasound acquisition and CIMT measurement procedures are described elsewhere[5,15-17] and in Supplemental Digital Content 1 (http://links.lww.com/MENO/A119).

Secondary Endpoints

Secondary endpoints include measurement of cognition and coronary artery atherosclerosis. Details of neuropsychological tests, procedures, and statistical analyses are described elsewhere.[11,18] Subclinical coronary artery atherosclerosis is assessed with cardiac CT scanning for coronary artery calcium (CAC) and with cardiac CT angiography (CCTA) for measurement of coronary artery stenoses in a single session using a dedicated cardiac GE 64-slice multidetector CT scanner as participants complete randomized treatment. CT endpoints represent a comprehensive assessment of coronary artery atherosclerosis across all of the coronary artery segments (total CAC, total stenosis score, total plaque score, and composition of coronary atherosclerotic plaque). Details of CAC and CCTA methods are described elsewhere[19,20] and in Supplemental Digital Content 1 (http://links.lww.com/MENO/A119).

Sample Size

Sample size was based on a projected mean (SD) treatment group difference in CIMT change rate (placebo-treated rate minus estradiol-treated rate) among women at less than 6 years since menopause (0.0144 [0.02] mm/y) and women at 10 years or more since menopause (0.0021 [0.02] mm/y). Sample size based on CIMT progression required 83 participants in each cell (126 participants per cell, including an anticipated 25% dropout) to detect treatment-by-time since menopause interaction in the 2 × 2 factorial design with 80% power, testing at a two-sided α of 0.05. This sample size was also projected to yield a power of 96% to detect a significant treatment group difference in CIMT progression rates in the early postmenopausal group.

Planned Statistical Analysis

Baseline comparisons with respect to demographics, medical history, baseline risk factors (blood pressure, smoking, and lipids), previous HT use, estradiol and progesterone levels, and baseline CIMT will be performed between treatment arms (within time since menopause strata). Analytical methods include two-sample t tests (or a nonparametric analog) for continuous variables and χ^2 tests for categorical variables. All treatment group comparisons on baseline variables will be performed for the entire randomized study sample and for the group of participants with repeated (postrandomization) carotid artery ultrasounds.

Evaluation of potential biases introduced by differential dropout (comparing participants with and participants without postrandomization ultrasound by treatment group) will be performed. Analytical methods will use standard univariate procedures for the total sample and time since menopause strata to compare these participant groups on baseline demographics and

baseline levels of laboratory and lifestyle variables.

On-trial levels of laboratory variables (plasma lipids, lipoproteins, glucose, hemoglobin A1c, estradiol, and progesterone) will be compared between treatment groups using marginal models with generalized estimating equations. Independent factors will include treatment group, time since menopause, and randomization stratification factors; baseline levels of on-trial dependent variables will be included as co-variates. The primary tests of interest will be the overall treatment group comparisons. Differences in the randomized treatment effect by menopause strata will also be determined, with the addition of a product interaction term. Statistical evaluations will report the overall test for treatment group difference, overall test for differences between time since menopause groups, and *P* value for interaction. Treatment group comparisons will be performed for the group of participants with any postrandomization carotid ultrasound and for adherent participants (adherent analysis). Defined as ≥80% compliance with estrogen therapy.

The primary endpoint is the per-participant rate of change in the right distal common carotid artery far wall intima-media thickness. Statistical analyses will use linear mixed-effects models; treatment group and time since menopause group will be included as indicator variables, with randomization stratification variables (type of menopause and dichotomous baseline CIMT) included as covariates. Random effects will be specified for participant-specific intercept (baseline CIMT) and slope (CIMT rate of change). The overall treatment group difference in mean CIMT rate will be tested with a two-way treatment group-by-time on study interaction. A two-way time-since menopause group-by-time on study interaction term will test whether the mean CIMT progression rate differs among the two postmenopause groups. The hypothesis that the treatment group effects on the CIMT rate differ by time since menopause will be tested with a time since menopause-by-treatment-by-time on study interaction term. Treatment group comparisons will be performed for the group of participants with any post-randomization carotid artery ultrasound and for adherent participants (≥80% compliance with estrogen therapy).

CAC and CCTA outcomes obtained at the end of the study (secondary trial endpoints) will be compared between treatment groups. Primary CCTA measures are total stenosis score and total plaque score, and secondary CCTA measures are number of coronary artery segments with calcified, noncalcified, and mixed plaques. CAC measures include the presence of any CAC (dichotomous variable) and CAC score. Generalized linear models—specifying these CAC and CCTA measures as dependent variables—will be used. The two randomization stratification variables (type of menopause and dichotomous baseline CIMT) will be included as covariates. To account for the fact that the end-of-study visit differs across participants, we will also include as covariates indicator variables for the study visit at which the CAC and CCTA measures are obtained. The primary independent variables of interest will be indicator variables for each of the study design factors, testing for differences in end-of-study CAC and CCTA measures by treatment group and menopause stratum. A treatment-by-menopause stratum interaction will test whether the treatment group differences differ by time since menopause. Treatment group comparisons will be performed for all participants who have the CAC and/or CCTA endpoints and for adherent participants (≥80% compliance with estrogen therapy).

Safety analysis and evaluation of adverse events will be performed on all randomized participants using exact methods-comparing events among the four study groups (early postmenopausal-estradiol-treated; early postmenopausal- placebo-treated; late postmenopausal-estradiol-treated; and late postmenopausal-placebo-treated)-because the primary question is whether any given group shows an elevated risk for adverse events. The following major clinical events will be evaluated and compared: (1) cardiovascular events (including fatal/nonfatal myocardial infarction [MI], silent MI, and sudden death), hospitalization for unstable angina, and coronary revascularization procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty); (2) stroke; (3) venous thromboembolism (deep vein thrombosis and pulmonary embolism); (4) cancer (breast, uterine, ovarian, gastrointestinal, and lung); (5) bone fractures; and (6) all-cause mortality and noncoronary mortality.

ELITE was approved by the Institutional Review Board of the University of Southern California. All participants provided a written informed consent form before trial-related procedures were conducted. Participant safety and trial conduct is overseen by an External Data Safety Monitoring Board (appointed by the National Institute on Aging, National Institutes of Health) with expertise in women's health, menopausal health, HT, CVD, clinical trials, and biostatistics.

Results

Recruitment and Screening

Recruitment for ELITE commenced in May 2005. The first participant was randomized on July 13, 2005; the last participant was randomized on September 30, 2008. A total of 643 participants were randomized. The original sample size estimates required randomization of 504 participants. Because response and recruitment to ELITE were large, a higher number of participants were

randomized to the trialVin particular women in the late postmenopausal groupVbecause previous HT use was high in this group and to compensate for any higher-thananticipated dropout rate in this older group.

To obtain 643 participants, we telephone-prescreened 2,166 candidates with a series of questions from a standard interview form. Of these 2,166 telephone-prescreened candidates, 1,271 were ineligible. The remaining 895 candidates were further screened during a clinic visit, from which the 643 participants were randomized. In total, 1,523 (70%) candidates were ineligible or refused enrollment. The primary reasons for ineligibility or refusal included current HT (171 women), 6 to 9 years postmenopausal (142 women), clinical signs or symptoms of CVD (81 women), diabetes or serum glucose level of 140 mg/dL or higher (21 women), history of breast cancer (37 women), and not postmenopausal by trial criteria (104 women).

Baseline Results

contrasts demographic factors and baseline examination results between the strata less than 6 years since menopause and 10 years or more since menopause. In the early postmenopausal stratum, the mean participant age was 55.4 years, and the median time since menopause was 3.5 years. In the late postmenopausal stratum, the mean participant age was 65.4 years, and the median time since menopause was 14.3 years. Overall, 32% of the women were from a minority racial or ethnic group, and 99% of the participants had a high school or greater education. Smoking history was similar between strata: 3.4% of the participants were active smokers and 37% of the participants were former smokers. As expected, hot flashes were more common in the early postmenopausal group relative to the late postmenopausal group. A major difference between strata was that more women in the late postmenopausal group previously used HT and were currently using antihypertensive and lipid-lowering medications, compared with women in the early postmenopausal group. More women in the late postmenopausal group underwent surgical menopause, compared with women in the early postmenopausal group (16.1% vs 3.3%, respectively).

Table 1. Demographic characteristics at baseline.

Characteristic	<6 y since menopause (n = 271)	≥10 y since menopause (n = 372)	*P* [a]
Age, mean (SD), y	55.4 (4.1)	65.4 (6.0)	<0.001
Time since menopause, median (interquartile range), y	3.5 (1.9-5.0) [n = 269]	14.3 (11.5-18.7) [n = 344]	<0.001
Race or ethnicity, n (%)			0.03
White, non-Hispanic	174 (64.2)	266 (71.5)	
Black, non-Hispanic	24 (8.9)	36 (9.7)	
Hispanic	41 (15.1)	49 (13.2)	
Asian	32 (11.8)	21 (5.7)	
Education, n (%)			0.05
College graduate	195 (72.0)	233 (62.6)	
High school or some college	75 (27.7)	137 (36.8)	
Less than high school	1 (0.4)	2 (0.5)	
Smoking history, n (%)			0.2
Current smoker	11 (4.1)	11 (3.0)	
Former smoker	89 (32.8)	147 (39.5)	
Never smoked	171 (63.1)	214 (57.5)	
Moderate or vigorous physical activity, mean (SD), hours during the past week[b]	7.0 (8.4)	5.5 (6.2)	0.01
Alcohol consumption (weekly estimate), n (%)			0.6
None	135 (49.8)	194 (52.2)	

>0 to 1 unit (15 g)/d	105 (38.8)	127 (34.1)	
>1 to 2 units (30 g)/d	23 (8.5)	39 (10.5)	
>2 units (>30 g)/d	8 (3.0)	12 (3.2)	
Type of menopause, n (%)			<0.001
Natural	262 (96.7)	312 (83.9)	
Surgical	9 (3.3)	60 (16.1)	
Hot flashes (any within previous month), n (%)[c]	173 (71.2) [n = 243]	157 (48.5) [n = 324]	<0.001
Number of hot flashes per day for women with any hot flashes, mean (SD)			
Mild	1.1 (1.7)	1.0 (1.4)	0.3
Moderate	1.1 (2.0)	1.2 (2.0)	0.8
Severe	0.62 (2.4)	0.55 (1.6)	0.7
Past use of hormone therapy, n (%)	138 (50.9)	321 (86.3)	<0.001
Current hypertension medications, n (%)	50 (18.5)	107 (28.8)	0.003
Current lipid-lowering medications, n (%)	40 (14.8)	88 (23.7)	0.005

[a]Statistical tests were performed using Student's two-sample *t* test for continuous variables, $\chi 2$ test for discrete variables, and Wilcoxon rank sum test for median time since menopause.

[b]Hours of moderate or vigorous physical activity (three or more standard metabolic equivalents) during the past 7 days.

[c]By hot flash diaries.

contrasts clinical, laboratory, and CIMT variables between time since menopause strata. The mean CIMT was greater among women in the late postmenopausal stratum than among women in the early postmenopausal stratum (0.787 vs 0.748 mm, respectively). Mean baseline systolic blood pressure was slightly greater and mean diastolic blood pressure was slightly lower among women in the late postmenopausal stratum relative to women in the early postmenopausal stratum. These mean blood pressure differences between the women in the two strata probably reflect greater baseline use of antihypertensive medications by women in the late postmenopausal stratum relative to women in the early postmenopausal stratum (28.8% vs 18.5%, respectively;). The slightly lower mean baseline fasting LDL-C level and higher HDL-C level among women in the late postmenopausal stratum relative to women in the early postmenopausal stratum, as well as the equivalence in baseline fasting plasma cholesterol and TG levels between strata ( ), probably reflects greater baseline use of lipid-lowering medications (most [96%] of which were from the statin class) among women in the late postmenopausal stratum relative to women in the early postmenopausal stratum (23.7% vs 14.8%, respectively;). Although the hemoglobin A1c value was slightly lower among women randomized to the early postmenopausal stratum relative to women randomized to the late postmenopausal stratum, fasting serum glucose level and body mass index (BMI) were equivalent between strata ( ).

Table 2. Clinical and laboratory characteristics at baseline.

Variable	<6 y since menopause (n = 271)	≥10 y since menopause (n = 372)	*P*
Carotid artery intima-media thickness, mm	0.748 (0.095)	0.787 (0.109)	<0.001
Body mass index, kg/m^2	27.2 (5.4)	27.4 (5.4)	0.7
Pulse rate, beats/min	65.5 (5.1)	66.1 (5.2)	0.1
Systolic blood pressure, mm Hg	116.8 (12.9)	118.7 (11.9)	0.06
Diastolic blood pressure, mm Hg	76.1 (7.1)	74.3 (7.0)	0.001
Serum lipids			

LDL-C, mg/dL	139.4 (32.1)	134.3 (30.8)	0.04
HDL-C, mg/dL	64.4 (16.0)	67.1 (18.6)	0.06
Total cholesterol, mg/dL	224.8 (33.9)	223.0 (33.4)	0.5
Triglycerides, mg/dL	105.1 (53.7)	108.0 (55.7)	0.5
Total cholesterol-to-HDL-C ratio	3.7 (1.1)	3.5 (1.0)	0.07
Glucose, mg/dL	95.5 (10.4)	94.5 (10.2)	0.2
Hemoglobin A1c, n (%)	5.5 (0.5) [n = 269]	5.7 (0.4) [n = 369]	0.002
Serum concentrations, median (interquartile range)			
Total estradiol, pg/mL	8.0 (5.8-11.4) [n = 271]	7.7 (5.8-10.5) [n = 372]	0.2
Free estradiol, pg/mL	0.20 (0.14-0.31) [n = 268]	0.18 (0.13-0.26) [n = 370]	0.04
Estrone, pg/mL	29.1 (22.7-38.1) [n = 269]	27.7 (20.2-37.1) [n = 372]	0.08
Progesterone, ng/mL	0.2 (<0.2-0.3) [n = 271]	0.2 (<0.2-0.3) [n = 370]	0.1
Total testosterone, ng/dL	20.5 (15.5-27.9) [n = 269]	21.6 (14.1-30.6) [n = 372]	0.4
Free testosterone, pg/dL	3.8 (2.9-5.5) [n = 268]	3.9 (2.8-5.7) [n = 370]	0.9
Sex hormone-binding globulin, nmol/L	46.1 (32.5-61.1) [n = 268]	51.1 (37.7-66.9) [n = 370]	0.01

All values are presented as mean (SD), unless otherwise stated.

Means between postmenopausal strata were compared using Student's two-sample *t* test. Medians were compared using Wilcoxon rank sum test.

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

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College graduate	195 (72.0)	233 (62.6)	
High school or some college	75 (27.7)	137 (36.8)	
Less than high school	1 (0.4)	2 (0.5)	
Smoking history, n (%)			0.2
Current smoker	11 (4.1)	11 (3.0)	
Former smoker	89 (32.8)	147 (39.5)	

Never smoked	171 (63.1)	214 (57.5)	
Moderate or vigorous physical activity, mean (SD), hours during the past week[b]	7.0 (8.4)	5.5 (6.2)	0.01
Alcohol consumption (weekly estimate), n (%)			0.6
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Hemoglobin A1c, n (%)	5.5 (0.5) [n = 269]	5.7 (0.4) [n = 369]	0.002
Serum concentrations, median (interquartile range)			
Total estradiol, pg/mL	8.0 (5.8-11.4) [n = 271]	7.7 (5.8-10.5) [n = 372]	0.2
Free estradiol, pg/mL	0.20 (0.14-0.31) [n = 268]	0.18 (0.13-0.26) [n = 370]	0.04
Estrone, pg/mL	29.1 (22.7-38.1) [n = 269]	27.7 (20.2-37.1) [n = 372]	0.08
Progesterone, ng/mL	0.2 (<0.2-0.3) [n = 271]	0.2 (<0.2-0.3) [n = 370]	0.1
Total testosterone, ng/dL	20.5 (15.5-27.9) [n = 269]	21.6 (14.1-30.6) [n = 372]	0.4
Free testosterone, pg/dL	3.8 (2.9-5.5) [n = 268]	3.9 (2.8-5.7) [n = 370]	0.9
Sex hormone-binding globulin, nmol/L	46.1 (32.5-61.1) [n = 268]	51.1 (37.7-66.9) [n = 370]	0.01

All values are presented as mean (SD), unless otherwise stated.

Means between postmenopausal strata were compared using Student's two-sample *t* test. Medians were compared using Wilcoxon rank sum test.

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 1. Demographic characteristics at baseline.

Characteristic	<6 y since menopause (n = 271)	≥10 y since menopause (n = 372)	*P* [a]
Age, mean (SD), y	55.4 (4.1)	65.4 (6.0)	<0.001
Time since menopause, median (interquartile range), y	3.5 (1.9-5.0) [n = 269]	14.3 (11.5-18.7) [n = 344]	<0.001
Race or ethnicity, n (%)			0.03
White, non-Hispanic	174 (64.2)	266 (71.5)	
Black, non-Hispanic	24 (8.9)	36 (9.7)	
Hispanic	41 (15.1)	49 (13.2)	
Asian	32 (11.8)	21 (5.7)	
Education, n (%)			0.05
College graduate	195 (72.0)	233 (62.6)	
High school or some college	75 (27.7)	137 (36.8)	
Less than high school	1 (0.4)	2 (0.5)	
Smoking history, n (%)			0.2
Current smoker	11 (4.1)	11 (3.0)	
Former smoker	89 (32.8)	147 (39.5)	
Never smoked	171 (63.1)	214 (57.5)	
Moderate or vigorous physical activity, mean (SD), hours during the past week[b]	7.0 (8.4)	5.5 (6.2)	0.01
Alcohol consumption (weekly estimate), n (%)			0.6

None	135 (49.8)	194 (52.2)	
>0 to 1 unit (15 g)/d	105 (38.8)	127 (34.1)	
>1 to 2 units (30 g)/d	23 (8.5)	39 (10.5)	
>2 units (>30 g)/d	8 (3.0)	12 (3.2)	
Type of menopause, n (%)			<0.001
Natural	262 (96.7)	312 (83.9)	
Surgical	9 (3.3)	60 (16.1)	
Hot flashes (any within previous month), n (%)[c]	173 (71.2) [n = 243]	157 (48.5) [n = 324]	<0.001
Number of hot flashes per day for women with any hot flashes, mean (SD)			
Mild	1.1 (1.7)	1.0 (1.4)	0.3
Moderate	1.1 (2.0)	1.2 (2.0)	0.8
Severe	0.62 (2.4)	0.55 (1.6)	0.7
Past use of hormone therapy, n (%)	138 (50.9)	321 (86.3)	<0.001
Current hypertension medications, n (%)	50 (18.5)	107 (28.8)	0.003
Current lipid-lowering medications, n (%)	40 (14.8)	88 (23.7)	0.005

[a]Statistical tests were performed using Student's two-sample *t* test for continuous variables, $\chi 2$ test for discrete variables, and Wilcoxon rank sum test for median time since menopause.

[b]Hours of moderate or vigorous physical activity (three or more standard metabolic equivalents) during the past 7 days.

[c]By hot flash diaries.

Table 2. Clinical and laboratory characteristics at baseline.

Variable	<6 y since menopause (n = 271)	≥10 y since menopause (n = 372)	*P*
Carotid artery intima-media thickness, mm	0.748 (0.095)	0.787 (0.109)	<0.001
Body mass index, kg/m^2	27.2 (5.4)	27.4 (5.4)	0.7
Pulse rate, beats/min	65.5 (5.1)	66.1 (5.2)	0.1
Systolic blood pressure, mm Hg	116.8 (12.9)	118.7 (11.9)	0.06
Diastolic blood pressure, mm Hg	76.1 (7.1)	74.3 (7.0)	0.001
Serum lipids			
LDL-C, mg/dL	139.4 (32.1)	134.3 (30.8)	0.04
HDL-C, mg/dL	64.4 (16.0)	67.1 (18.6)	0.06
Total cholesterol, mg/dL	224.8 (33.9)	223.0 (33.4)	0.5
Triglycerides, mg/dL	105.1 (53.7)	108.0 (55.7)	0.5
Total cholesterol-to-HDL-C ratio	3.7 (1.1)	3.5 (1.0)	0.07
Glucose, mg/dL	95.5 (10.4)	94.5 (10.2)	0.2
Hemoglobin A1c, n (%)	5.5 (0.5) [n = 269]	5.7 (0.4) [n = 369]	0.002
Serum concentrations, median (interquartile range)			
Total estradiol, pg/mL	8.0 (5.8-11.4) [n = 271]	7.7 (5.8-10.5) [n = 372]	0.2

Free estradiol, pg/mL	0.20 (0.14-0.31) [n = 268]	0.18 (0.13-0.26) [n = 370]	0.04
Estrone, pg/mL	29.1 (22.7-38.1) [n = 269]	27.7 (20.2-37.1) [n = 372]	0.08
Progesterone, ng/mL	0.2 (<0.2-0.3) [n = 271]	0.2 (<0.2-0.3) [n = 370]	0.1
Total testosterone, ng/dL	20.5 (15.5-27.9) [n = 269]	21.6 (14.1-30.6) [n = 372]	0.4
Free testosterone, pg/dL	3.8 (2.9-5.5) [n = 268]	3.9 (2.8-5.7) [n = 370]	0.9
Sex hormone-binding globulin, nmol/L	46.1 (32.5-61.1) [n = 268]	51.1 (37.7-66.9) [n = 370]	0.01

All values are presented as mean (SD), unless otherwise stated.

Means between postmenopausal strata were compared using Student's two-sample *t* test. Medians were compared using Wilcoxon rank sum test.

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

shows the age- and race-adjusted linear associations of CIMT with baseline characteristics according to postmenopausal strata. The mean (SE) CIMT increased by 0.026 (0.003) mm for every 5-year increase in age ($P < 0.001$). As expected, the cardiovascular risk factors blood pressure and BMI were positively associated with CIMT in both strata. The mean (SE) CIMT increased by 0.002 (0.0004) mm for every 1-mm Hg increase in systolic blood pressure in the early postmenopausal stratum, by 0.002 (0.0005) mm for every 1-mm Hg increase in systolic blood pressure in the late postmenopausal stratum, by 0.002 (0.0008) mm for every 1-mm Hg increase in diastolic blood pressure in the early postmenopausal stratum, and by 0.002 (0.0008) mm for every 1-mm Hg increase in diastolic blood pressure in the late postmenopausal stratum. The mean (SE) CIMT increased by 0.002 (0.001) mm for every 1-kg/m^2 increase in BMI in the early postmenopausal stratum and by 0.003 (0.001) mm for every 1-kg/$m^{[2]}$ increase in BMI in the late postmenopausal stratum. Type of menopause (surgical vs natural), LDL-C, TG, TC-to-HDL-C ratio, HDL-C (inverse), total testosterone (inverse), and SHBG (inverse) were associated with CIMT in the early postmenopausal stratum but not in the late postmenopausal stratum, although the interaction between strata for these variables was not statistically significant. In the early postmenopausal stratum, the mean (SE) CIMT increased by 0.073 (0.030) mm for surgical versus natural menopause, by 0.0004 (0.0002) mm for every 1-mg/dL increase in LDL-C, by 0.066 (0.028) mm for every unit increase in log TG (mg/dL), and by 0.018 (0.005) mm for every 1-unit increase in TC-to-HDL-C ratio; the mean CIMT decreased by 0.001 (0.0003) mm for every 1-mg/dL increase in HDL-C, by 0.054 (0.027) mm for every unit increase in log total testosterone (ng/dL), and by 0.082 (0.027) mm for every unit increase in log SHBG (nmol/L). CIMT associations with pulse rate and serum levels of total estradiol differed across strata (*P* for interaction = 0.02). Serum total estradiol was negatively associated with CIMT (mean [SE] CIMT decrease of 0.032 [0.019] mm for every unit increase in log total estradiol (pg/mL), $P = 0.09$) among women randomized to the early postmenopausal stratum but not among women randomized to the late postmenopausal stratum. A higher pulse rate was positively associated with CIMT in the early postmenopausal stratum (mean [SE] CIMT increase by 0.003 [0.001] mm for every 1-beat per minute increase in heart rate, $P = 0.002$) but not in the late postmenopausal stratum.

Table 3. Baseline associations with carotid artery intima-media thickness.

Characteristic	<6 y since menopause (n = 271)		≥10 y since menopause (n = 372)		*P* for interaction
	β (SE)	*P*	*β* (SE)	*P*	
Education					
College graduate	Ref	0.9	Ref	0.5	0.8
High school or some college	−0.003 (0.012)		−0.007 (0.011)		
Less than high school	−0.011 (0.089)		0.080 (0.075)		
Current smoker	−0.007 (0.027)	0.8	0.003 (0.032)	0.9	0.8
Moderate or vigorous physical activity[a]					
None	Ref	0.4	Ref	0.3	0.2

0.1-2.9 h/wk	0.033 (0.021)		−0.030 (0.019)		
3.0-6.9 h/wk	0.014 (0.021)		−0.023 (0.019)		
≥7.0 h/wk	0.020 (0.021)		−0.008 (0.019)		
Alcohol consumption					
None	Ref	0.9	Ref	0.2	0.8
>0 to 1 unit (15 g)/d	−0.006 (0.12)		−0.023 (0.012)		
>1 to 2 units (30 g)/d	0.003 (0.020)		0.007 (0.018)		
>2 units (>30 g)/d	−0.021 (0.032)		−0.024 (0.031)		
Type of menopause					
Natural	Ref	0.02	Ref	0.5	0.06
Surgical	0.073 (0.030)		−0.011 (0.015)		
Hot flashes (any within previous month)[b]	0.0006 (0.013)	0.9	−0.002 (0.012)	0.9	0.9
Past use of hormone therapy	−0.007 (0.011)	0.5	−0.026 (0.016)	0.09	0.3
Current hypertension medications	0.005 (0.014)	0.7	0.004 (0.012)	0.8	0.9
Current lipid-lowering medications	0.017 (0.015)	0.3	0.0003 (0.013)	0.9	0.4
Body mass index	0.002 (0.001)	0.02	0.003 (0.001)	0.007	0.4
Pulse rate	0.003 (0.001)	0.002	−0.0003 (0.001)	0.8	0.02
Systolic blood pressure	0.002 (0.0004)	<0.001	0.002 (0.0005)	<0.001	0.7
Diastolic blood pressure	0.002 (0.0008)	0.02	0.002 (0.0008)	0.05	0.8
Serum lipids					
LDL-C	0.0004 (0.0002)	0.02	0.0003 (0.0002)	0.1	0.8
HDL-C	−0.001 (0.0003)	0.005	−0.0004 (0.0003)	0.2	0.3
Total cholesterol	0.0002 (0.0002)	0.1	0.0001 (0.0002)	0.5	0.6
Triglycerides[c]	0.066 (0.028)	0.02	0.0009 (0.030)	0.9	0.1
Total cholesterol-to-HDL-C ratio	0.018 (0.005)	<:0.001	0.010 (0.005)	0.06	0.4
Glucose	0.0006 (0.0005)	0.2	0.0007 (0.0005)	0.2	0.9
Hemoglobin A1c	0.006 (0.011) [n = 269]	0.6	−0.010 (0.014) [n = 369]	0.4	0.4
Total estradiol	−0.032 (0.019) [n = 271][c]	0.09	0.037 (0.026) [n = 372]	0.2	0.02
Free estradiol	−0.014 (0.018) [n = 268][c]	0.4	0.032 (0.023) [n = 370]	0.2	0.06
Estrone	−0.039 (0.030) [n = 269][c]	0.2	0.004 (0.030) [n = 372]	0.9	0.3
Progesterone					
<0.2 ng/mL	Ref	0.9	Ref	0.5	0.8
0.2 ng/mL	0.007 (0.015) [n = 271]		0.013 (0.014) [n = 370]		

0.3 ng/mL	0.002 (0.015) [n = 271]		0.0007 (0.016) [n = 370]		
>0.3 ng/mL	0.003 (0.016) [n = 271]		0.021 (0.016) [n = 370]		
Total testosterone[c]	−0.054 (0.027) [n = 269]	0.05	0.0008 (0.023) [n = 372]	0.9	0.2
Free testosterone[c]	−0.014 (0.026) [n = 268]	0.6	0.009 (0.023) [n = 370]	0.7	0.5
Sex hormone-binding globulin[c]	−0.082 (0.027) [n = 268]	0.002	−0.010 (0.028) [n = 370]	0.7	0.1

For categorical variables, β is the mean difference in carotid artery intima-media thickness from the specified referent group. For continuous variables, β is the mean difference in carotid artery intima-media thickness per unit change in the relevant variable.

Multiple linear regression analyses were conducted for each variable, adjusting for age and race.

Ref, referent; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

[a]Hours of moderate or vigorous physical activity (three or more standard metabolic equivalents) during the past 7 days.

[b]By hot flash diaries.

[c]Log-transformed.

Discussion

Results of the recruitment, screening, and randomization phases of ELITE indicate that the design and implementation produced baseline conditions that are well-suited for a randomized controlled trial testing the timing hypothesis of HT on vascular disease and cognition. By design, there is excellent separation without overlap in time since menopause between the group of women at less than 6 years since menopause (median, 3.5 y) and the group of women at 10 years or more since menopause (median, 14.3 y). This outcome provides an optimal setting in which we are able to determine the effects of HT on atherosclerosis progression, CAD, and cognitive changes in strata of women with characteristics similar to those described in key studies. The early postmenopausal group is representative of postmenopausal women initiating HT in clinical practice near the time of menopause. Demographic and health risk factors are similar to those found in most observational studies of HT use[21,22] and in the Danish Osteoporosis Prevention Study (DOPS) randomized trial.[23] The late postmenopausal group is more comparable to the entire cohort of women in the WHI, in which participants were, on average, aged 64 years and had been postmenopausal for 12 years at randomization.[1] Baseline CVD risk factors across postmenopausal strata (such as smoking, BMI, blood pressure, lipids, glucose, and hemoglobin A1c) are similar, whereas baseline CIMT value is lower in the early postmenopausal group relative to the late postmenopausal group. Baseline use of lipid-lowering and antihypertensive medications is greater in the late postmenopausal group than in the early postmenopausal group.

Although traditional and expected risk factor associations with CIMT (age, blood pressure, and BMI) are present at baseline in both time since menopause strata (<6 y and ≥10 y since menopause), several important associations evident in the early postmenopausal group, but not in the late postmenopausal group, may have relevance to the timing hypothesis and may play a role in the responsiveness of atherosclerosis progression to HT. Of these differences, perhaps the most important are the significant positive LDL-C association and inverse HDL-C and SHBG associations with baseline CIMT in the early postmenopausal group. We have previously shown that the LDLC-lowering and HDL-C-raising effects of HT account for 30% of the effects of randomized HT on reducing atherosclerosis progression.[24] The statistically significant inverse association of SHBG with CIMT in the early postmenopausal group may be of particular importance, as we have previously shown that the HT-related reduction in atherosclerosis progression occurs in women showing an increase in SHBG in response to HT.[25] The significant interaction across postmenopausal strata for total serum estradiol levels and CIMT seems consistent with the timing hypothesis. The statistically significant, inverse association of total serum estradiol levels (in the relatively restricted range of postmenopausal levels) with CIMT in the early postmenopausal group supports our prediction that raising estradiol levels may decrease progression of atherosclerosis in this group of women. In the late postmenopausal group, total serum estradiol levels

show no association with CIMT, suggesting that raising estradiol levels may have no effect on atherosclerosis progression in this group of women. Whether these differential risk factor associations with CIMT at baseline (according to strata) play a role in determining whether HT reduces atherosclerosis progression in women who had been postmenopausal for less than 6 years, relative to women who had been postmenopausal for 10 years or more, remains to be determined. Although the strata are sufficiently separated according to time since menopause, certain baseline factors could obscure our results and the timing hypothesis for this trial. One possible variable is age; age and time since menopause tend to covary, and the variable that may be a stronger factor in determining the potential responsiveness of atherosclerosis progression to HT has not been determined. Although there is a baseline mean 10-year difference in age between postmenopausal strata, there is substantial overlap in age across strata.

With the beneficial effects of HT for reducing atherosclerosis progression (reported in EPAT in 2001), we hypothesized that intervention early in the atherosclerosis process at the start of menopause may be the key to CVD prevention with HT.[5] This led to the hypothesis that HT may be more effective as primary prevention when initiated in the early stages of atherosclerosis rather than as secondary prevention when atherosclerosis has been established.[6] HT may be effective in the prevention, but not in the treatment, of vascular disease.[6] With the publication of EPAT's sister study WELL-HART, where the effect of HT on established atherosclerosis was null, we concluded that the difference in outcomes between the two trials (EPAT and WELL-HART) may have resulted from the timing of the intervention relative to the stage of atherosclerosis, as measured by the different imaging methods used in these trials[6] (carotid artery wall thickness in EPAT as a measure of early, asymptomatic, subclinical atherosclerosis; quantitative coronary angiography in WELL-HART to evaluate late-stage symptomatic atherosclerosis).[5,6] In support of these human trial findings, accumulating literature from animal studies has shown that estrogen has little effect on reversing atherosclerosis once it is established, whereas it significantly reduces the extent of atherosclerosis if therapy is initiated at the early stage of atherosclerosis development.[7-9]

Since 2001, there has been a large accumulation of data from randomized trials strongly supporting the timing hypothesis (Table 4), suggesting that women respond differentially to HT according to the timing of HT initiation relative to age and/or time since menopause, particularly with regard to CHD outcomes.[1] Meta-analyses of accumulated data have shown that the effect of HT on CHD and total mortality is null when HT is initiated in women older than 60 years and/or more than 10 years since menopause, whereas when HT is initiated in women younger than 60 years and/or less than 10 years since menopause, there is a 32% reduction in CHD and a 39% reduction in total mortality relative to placebo.[26-28,31] The magnitude of CHD and total mortality reduction for women younger than 60 years and/or who had been postmenopausal for less than 10 years upon randomization to HT is similar to observational studies of populations of women who initiated HT at or near the time of menopause.[21,22]

In a more recent randomized trial with a PROBE (prospectively, randomized, open with blinded endpoint evaluation) design, DOPS provided data for the long-term use of oral estradiol alone and estradiol with sequential norethisterone acetate when initiated in healthy young perimenopausal and early postmenopausal women.[23] DOPS included 1,006 postmenopausal women who were, on average, aged 50 years and had been postmenopausal for 7 months. The composite primary trial endpoint of mortality, MI, or heart failure was significantly reduced by 52% (hazard ratio [HR], 0.48; 95% CI, 0.27-0.89) and by 39% (HR, 0.61; 95% CI, 0.39-0.94) after 10 years of randomized treatment and 16 years of total follow-up (10 y of randomized treatment and 6 y of postintervention follow-up), respectively. Total mortality was reduced by 43% (HR, 0.57; 95% CI, 0.30-1.08) after 10 years of randomized treatment and by 34% (HR, 0.66; 95% CI, 0.41-1.08) after 16 years of total follow-up. Similar to DOPS are the 11-year WHI trial follow-up (7 y of randomized treatment and 4 y of postintervention follow-up) data. In the WHI, women without intact uterus who were aged 50 to 59 years upon randomization to conjugated equine estrogens (CEE) had significant reductions, relative to placebo, in CHD (41%; HR, 0.59; icant reductions, relative to placebo, in CHD (41%; HR, 0.59; icant reductions, relative to placebo, in CHD (41%; HR, 0.59; 1.00).[29] These treatment outcomes significantly differed by age, with reduction in risk among younger postmenopausal women and increased risk among older postmenopausal women (*P* for interaction: $P = 0.05$ for CHD, $P = 0.007$ for MI, and $P = 0.04$ for total mortality, respectively). Findings thus indicate that the effects of CEE on these outcomes differed by age at HT initiation.[29]

Other evidence that HT initiation in young postmenopausal women near menopause may reduce CHD derives from 1,064 women who participated in the WHI CAC substudy, in which women aged 50 to 59 years who were randomized to CEE had significantly less CAC on year 7 of the trial compared with women randomized to placebo.[32] There was no older age group in this substudy to evaluate whether HT influenced CAC when initiated in women older than 60 years. Results of ELITE will provide the necessary data to determine the effect of HT on CAC in younger postmenopausal women with HT initiation near menopause relative to older postmenopausal women with HT initiation distant from menopause. In addition, for the first time, the effects of

HT on CAD will be determined with CCTA in an asymptomatic population of women in ELITE. The Kronos Early Estrogen Prevention Study provided data for CIMT and CAC with low-dose HT in a select group of low-risk women (CACG50 Agatston units at baseline) randomized within 3 years of menopause.

In addition to mammalian hormones, other agents that bind to the estrogen receptor exert similar CHD beneficial effects on young postmenopausal women as HT. Among women who were younger than 60 years upon randomization to raloxifene (a selective estrogen receptor modulator), CHD was significantly reduced by 41% (HR, 0.59; 95% CI, 0.41-0.83) relative to placebo.[30] Women older than 60 years showed no benefit from raloxifene. In the Women's Isoflavone Soy Health study, a randomized controlled trial in which the effects of high-dose isoflavone soy protein supplementation (plant estrogens that preferentially bind to estrogen receptorA) on the progression of subclinical atherosclerosis were determined, women who were randomized to isoflavone soy protein supplementation within 5 years of menopause had a significant reduction in the progression of subclinical atherosclerosis relative to placebo, whereas isoflavone supplementation among women who had been postmenopausal for more than 5 years at randomization had no significant effect.[33]

Conclusions

The randomized trial data show that HT reduces the incidence of CHD and total mortality in young postmenopausal women (younger than 60 y) who initiate HT near menopause (< 10 y since menopause;).[1] These findings are consistent with the reductions in CHD and total mortality reported from observational studies, where most women initiated HT within 6 years of menopause.[21,22] Although the cumulative literature is more than suggestive of this conclusion, no clinical trial has specifically tested the timing hypothesis with regard to CHD or cognitive outcomes. In this respect, ELITE is both timely and unique. During the past decade, the timing hypothesis pertaining to CHD has matured into a well-supported hypothesis awaiting more definitive study. For cognitive decline in the absence of dementia, the timing hypothesis remains of critical concern,[34] although supportive data are less fully developed than for CHD. As postrandomization baseline data indicate, ELITE is well-positioned to test the timing hypothesis of HT in relation to atherosclerosis progression, CAD, and cognitive changes.

Table 4. Coronary heart disease and total mortality in women initiating hormone or selective estrogen receptor modifier therapy before age 60 years and/or within 10 years of menopause.

Studies	Age (y)	Time since menopause	Hormone therapy	Coronary heart disease		Total mortality	
				% Reduction	Risk ratio	(95% CI) % Reduction	Risk ratio (95% CI)
Meta-analysis[26]	<60	<10 y		↓ 32	0.68 (0.48-0.96)		
Meta-analysis[27]	54					↓ 39	0.61 (0.39-0.95)
Bayesian meta-analysis[28]	55					↓ 27	0.73 (0.52-0.96)
Observational studies[21,22]	30-55	<5 y		↓ 30-50		↓ 20-60	
DOPS, 10 y[23]	50	7 mo	E2 alone and E2 + NETA sequential	↓52	0.48 (0.27-0.89)	↓ 43	0.57 (0.30-1.08)
DOPS, 16 y[23]				↓ 39	0.61 (0.39-0.94)	↓ 34	0.66 (0.41-1.08)
WHI-E, 11 y[29]	<60		CEE alone	↓ 41	0.59 (0.38-0.90)	↓ 27	0.73 (0.53-1.00)

WHI-E[10]		<10 y	CEE alone	↓ 52	0.48 (0.20-1.17)	↓ 35	0.65 (0.33-1.29)
WHI-E + P[10]		<10 y	CEE + MPA continuous combined	↓ 12	0.88 (0.54-1.43)	↓ 19	0.81 (0.52-1.24)
WHI-E[10]	<60		CEE alone	↓ 37	0.63 (0.36-1.09)	↓ 29	0.71 (0.46-1.11)
WHI-E + P[10]	<60		CEE + MPA continuous combined	↑ 29	1.29 (0.79-2.12)	↓ 31	0.69 (0.44-1.07)
RUTH[30]	<60		Raloxifene	↓ 41	0.59 (0.41-0.83)		

DOPS, Danish Osteoporosis Prevention Study; E2, estradiol; NETA, norethisterone acetate; WHI-E, Women's Health Initiative estrogen-alone trial; CEE, conjugated equine estrogens; WHI-E + P, Women's Health Initiative estrogen + progestin continuous-combined trial; MPA, medroxyprogesterone acetate; RUTH, Raloxifene Use for the Heart trial.

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