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A systematic review and meta-regression analysis to examine the 'timing hypothesis' of hormone replacement therapy on mortality, coronary heart disease, and stroke☆

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ABSTRACT

Background: The 'Timing Hypothesis' states that the benefits and harms of hormone replacement therapy (HRT) are related to the proximity with which it is begun following the onset of menopause. The primary aim of this analysis was to test for heterogeneity of treatment effect for HRT using Chi^2 and I^2 tests for younger versus older initiators of HRT. The secondary aim was to perform a meta-regression with mean age at trial baseline as the covariate for various outcomes.

Methods: Younger initiation trials were defined as those with mean age of participants <60 years and older initiation trials were those with mean age >60 years. The primary endpoints included all-cause mortality, cardiac mortality, coronary heart disease (CHD) events (a composite of cardiac mortality and nonfatal myocardial (MI)), and a composite of stroke, transient ischemic attack (TIA) and systemic embolism.

Results: Thirty-one RCTs were identified comparing HRT users to nonusers ($n = 40{,}521$). There was significant heterogeneity of treatment effect between younger versus older HRT initiators for all-cause mortality ($Chi^2 = 9.74$, $p = 0.002$, $I^2 = 89.7\%$), cardiac mortality ($Chi^2 = 4.04$, $p = 0.04$, $I^2 = 75.2\%$), and CHD events ($Chi^2 = 3.06$, $p = 0.08$, $I^2 = 67.3\%$). Both groups experienced an increase in stroke, TIA and systemic embolism (1112/18,774 in the HRT group versus 734/18,070 in the control group; OR = 1.52; 95% confidence interval (CI) = 1.38–1.67). When performing the meta-regression, as age increased the treatment effect of HRT was increased for stroke, TIA and systemic embolism (point estimate 0.006 with a standard error of 0.002) ($p = 0.0003$).

Conclusion: Younger initiation of HRT may be effective in reducing death and cardiac events. However, younger HRT initiators remained at an increased risk of stroke, TIA and systemic embolism and this risk increased as average age increased. Younger menopausal women using HRT to treat vasomotor symptoms do not appear to be at an increased risk of dying or experiencing CHD events.

1. Introduction

The 'Timing Hypothesis' states that the benefits and harms of hormone replacement therapy (HRT) are related to the proximity with which it is begun following the onset of menopause [1,2]. A recent randomized trial tested the cardiovascular effects of the timing hypothesis. Prior to this study, the effects of HRT timing had not been previously studied in humans in a primary prespecified manner. In the trial, 643 healthy post-menopausal women were stratified into 2 groups based on time since menopause (<6 years versus ≥10 years since the onset of menopause) and randomized to receive either HRT or placebo. After a median of 5 years of follow-up, the rate of change of carotid intima media thickness (CIMT) was significantly reduced in younger women taking HRT when compared to placebo. In older women, there was no difference in CIMT rate of change between HRT and placebo. This study was small and underpowered to detect differences in hard outcomes including cardiovascular disease (CVD) events or all-cause mortality, but its main findings support the timing hypothesis and HRT's potential protective role in vascular health among younger postmenopausal women [3]. Current recommendations from the United States Preventative Task Force (USPTF) do not support HRT for either primary or secondary prevention of chronic medical conditions including CVD in both younger and older postmenopausal women [4]. The objective of this study is to perform a meta-

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analysis to examine the timing hypothesis. The primary aim of this analysis was to test for heterogeneity of treatment effect of HRT using Chi^2 and I^2 tests in younger versus older initiators of HRT on all-cause mortality, cardiac mortality, coronary heart disease (CHD) events and stroke, TIA and systemic embolism. The secondary aim of this analysis is to perform a meta-regression on each endpoint using mean age as the covariate.

2. Methods

The Preferred Reporting Items for Systemic Reviews and Meta-Analysis statement was followed [5,6]. A search was performed to identify all prospective randomized controlled trials (RCTs) which used systemic HRT in women and analyzed various health outcomes. Relevant English language articles were found by searching the electronic database PubMed (1979–2017) with search terms corresponding to "hormone replacement therapy". The PubMed search syntax used is as follows: ("comparative study" [Publication Type] OR "comparative study" [All Fields]) AND ("hormones" [Pharmacological Action] OR "hormones" [MeSH Terms] OR "hormones" [All Fields] OR "hormone" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields]) AND ("postmenopause" [MeSH Terms] OR "postmenopause" [All Fields]) AND ("cardiovascular system" [MeSH Terms] OR ("cardiovascular" [All Fields] AND "system" [All Fields]) OR "cardiovascular system" [All Fields] OR "cardiovascular" [All Fields]). The references of all articles retrieved were searched.

RCTs testing daily systemic HRT (either estrogen alone or combined estrogen plus progesterone) were considered for inclusion. If one of the primary endpoints of this meta-analysis was reported the trial was included. RCTs which compared HRT to placebo or to nonusers of HRT were eligible for inclusion. Interventions included estrogen alone and combined estrogen plus progesterone. The primary endpoints for this study included all-cause mortality, cardiac mortality, coronary heart events (a composite of cardiac mortality and nonfatal myocardial infarction (MI)), and a composite of stroke, transient ischemic attack (TIA) and systemic embolism. These endpoints were pre-specified as primary outcomes of the analysis.

One author (MN) searched all titles and abstracts. All articles were evaluated by both authors to assess if the study meets the inclusion criteria (Fig. 1). Data was independently extracted from the RCTs in a standardized manner. The following outcomes were extracted from each trial: all-cause mortality, cardiac mortality, nonfatal MI, stroke, transient ischemic attack, pulmonary embolism or deep venous thrombosis. The average age and number of women at the start of each trial

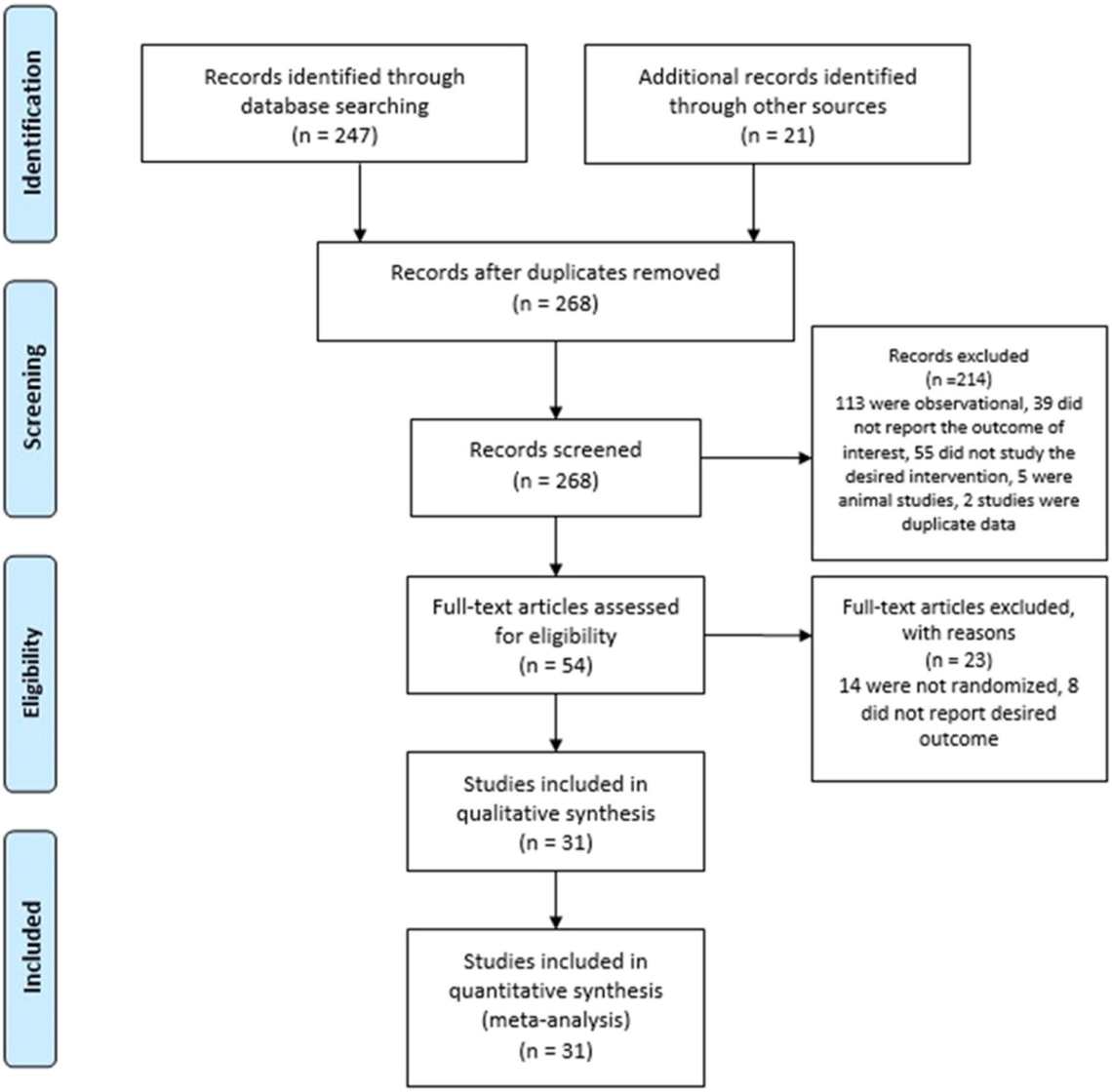

Fig. 1. PRISMA flow diagram. The flow diagram shows the study selection process including the number of studies screened, the number of studies excluded and reasons for exclusion of studies.

was collected. The average follow-up time and formulation of HRT used in each trial was recorded (Table 1). All studies included were assessed for bias by using the Cochrane Handbook for Systematic Review of Interventions by both authors [7]. Bias was assessed on predetermined criteria including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other (i.e. predetermined outcome of trial, financial consideration).

The primary analysis was conducted with the Mantel-Haenszel method. Summary odds ratio (OR) with 95% confidence interval (CI) were calculated using a random effects model. Examination of heterogeneity was performed using Q statistics and I^2. The 95% CIs were estimated using binominal distribution. A subgroup analysis was performed based on the average age of trial participants. Younger initiation trials were defined as those where the mean age of participants was <60 years and older initiation trials were those where the mean age was >60 years. Heterogeneity was analyzed for each outcome overall and for each subgroup. A meta-regression was performed using mean age at trial baseline as the covariate. Given that the incidence of some endpoints was zero, a previously described arcsine method [8] was used for performing both a random and fixed effects meta-regression. A sensitivity analysis was performed for each endpoint that excluded open-label RCTs. Also, another sensitivity analysis was performed which excluded the Women's Health Initiative Hormone Therapy (WHI-HT) trial from the analysis. This is the largest trial and has the most weight in the analysis. This was done to ensure that any subgroup differences found were not affected when excluding this study. Publication bias was assessed using funnel plots. All statistical analyses were conducted with Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. The *p*-values were 2-sided and an alpha value of 0.05 was considered to be statistically significant.

3. Results

Twenty-eight RCTs [3,9–35] including 38,367 participants were identified that reported at least one death from any cause. The mean age of participants in these trials was 62.3 years. The mean (±SD) follow up duration of RCTs was 3.83 ± 0.53 years. The risk of bias was judged to be low to moderate as 39 out of 196 (20%) domains were determined to be high or questionable bias (eTable 1). Six of the included RCTs in the primary analysis were open-label [10,12,20–23]. Overall, there were 885/19,581 (4.5%) deaths in the HRT group and 867/18,786 (4.6%) deaths in the control group with an OR of 1.01 [95% CI, 0.91–1.11] (Fig. 2).

For older HRT initiators, thirteen RCTs were identified with 25,577 participants. The mean age among older initiators was 66.9 years. The mean trial duration was 3.2 ± 0.47 years. All-cause mortality in older initiators was 735/12,897 (5.7%) in HRT users versus 670/12,680 (5.3%) in the control group with an OR of 1.08 [95% CI, 0.97–1.21]. There was no significant heterogeneity noted among RCTs with older HRT initiators (Chi = 5.78, $p = 0.93$, $I^2 = 0\%$). For younger initiators, sixteen RCTs were identified with 12,790 participants. The mean age was 54.5 years. The mean trial duration was 4.35 ± 0.9 years. All-cause mortality among younger HRT initiators was 150/6684 (2.2%) in HRT users compared to 197/6106 (3.2%) in the control group with an OR of 0.72 [95% CI, 0.57–0.91]. There was no heterogeneity among younger initiator trials ($Chi^2 = 5.78$, $p = 0.93$, $I^2 = 0\%$). When performing the test for subgroup differences, there was significant heterogeneity of treatment effect noted between younger versus older HRT initiators for all-cause mortality ($Chi^2 = 9.74$, $p = 0.002$, $I^2 = 89.7\%$) (Fig. 2). When excluding all open-label trials in a sensitivity analysis [10,12,20–23], there was still significant heterogeneity of treatment effect noted between younger and older initiators of HRT and all-cause mortality ($Chi^2 = 7.47$, $p = 0.006$, $I^2 = 86.6\%$). When excluding the WHI-HT trial this subgroup difference based on age was still present but was no longer statistically significant ($Chi^2 = 3.14$, $p = 0.08$, $I^2 = 68.1$). When performing the fixed effect regression for all-cause mortality the intercept point estimate was −0.26 with a standard error of 0.11 ($p = 0.01$). For mean age, the point estimate was 0.004 with a standard error of 0.002 ($p = 0.02$). When using a random effects model for the regression analysis the intercept point estimate was −0.01 with a standard error of 0.22 ($p = 0.64$). For mean age the point estimate was 0.002 with a standard error of 0.004 ($p = 0.63$).

In total, twenty-two RCTs [3,10,13–15,18–20,22,24,25,28–34,36,37] with 36,262 participants were identified that reported at least one CHD event. The mean age of participants was 63.0 years and the mean trial duration was 3.71 ± 0.58 years. The risk of bias among studies which reported a CHD event was judged to be low to moderate with 23 out of 154 (15%) domains having high or questionable bias (eTable 1). Four included RCTs were open-label [10,20,22,36]. There were 717/18,538 (3.9%) reported CHD events in the experimental group and 679/17,724 (3.8%) reported CHD events in the control group with an OR of 1.01 [95% CI, 0.91–1.13]. There was no heterogeneity found between the trials ($Chi^2 = 20.58$, $p = 0.49$, $I^2 = 0\%$) (eFigure 1). For older HRT initiators, twelve RCTs were identified with 24,561 participants and the mean trial duration (±SD) was 3.35 ± 0.49 years. The mean age of older HRT initiators was 67.1 years. Among older HRT initiators, CHD events occurred in 645/12,442 (5.2%) compared to 587/12,119 (4.8%) in the control group with an OR of 1.05 [95% CI, 0.93–1.18]. There was no statistical heterogeneity found between older initiator only trials ($Chi^2 = 6.66$, $p = 0.83$, $I^2 = 0\%$). In the younger initiator group, eleven RCTs were identified with 11,701 participants with a mean age of 54.3 years. The mean trial duration was 4.6 ± 1.06 years. There were 72/6096 (1.2%) CHD events reported in younger HRT initiator group and 92/5605 (1.6%) CHD events reported in the control group with an OR of 0.61 [95% CI, 0.37–1.00]. There was no statistical heterogeneity observed in the younger initiator trials ($Chi^2 = 6.42$, $p = 0.49$, $I^2 = 0\%$) (eFigure 1). When performing the test for subgroup differences, there was significant heterogeneity found between younger versus older HRT users for CHD events ($Chi^2 = 4.04$, $p = 0.04$, $I^2 = 75.2\%$). In a sensitivity analysis excluding open-label trials [10,20,22,36], there was no heterogeneity found between younger and older initiators of HRT and CHD events ($Chi^2 = 0.57$, $p = 0.45$, $I^2 = 0\%$). The reduced risk of CHD events among younger HRT initiators was no longer present when excluding the open-label RCTs (OR 0.91 [95% CI, 0.65–1.29]). When excluding the WHI-HT trial there was still heterogeneity observed between younger and older initiators of HRT and CHD events ($Chi^2 = 7.15$, $p = 0.007$, $I^2 = 86.0$). When performing the fixed effect regression for CHD events the intercept point estimate was −0.21 with a standard error of 0.11 ($p = 0.06$). For mean age, the point estimate was 0.003 with a standard error of 0.002 ($p = 0.05$). When using a random effects model for the regression analysis the intercept point estimate was −0.32 with a standard error of 0.22 ($p = 0.15$). For mean age the point estimate was 0.005 with a standard error of 0.004 ($p = 0.16$).

For cardiac mortality, seventeen RCTs [10,14,15,18–20,22,24–32,34] were identified with 35,042 participants. The mean trial duration was 3.84 ± 0.73 years and the mean age of participants was 63.2 years. The bias was judged to be low to moderate with 21 of 119 (18%) domains meeting the criteria for high or questionable bias (eTable 1). Three of the included RCTs were open-label [12,20,22]. Among all HRT users, cardiac death rate was 319/17,749 (1.8%) compared to control group cardiac death rate of 317/17,293 (1.8%) with an OR of 0.94 [95% CI, 0.76–1.17]. There was no significant statistical heterogeneity noted in all trials that reported cardiac death ($Chi^2 = 18.19$, $p = 0.31$, $I^2 = 12\%$). For older initiators, nine RCTs with 24,267 participants were analyzed with a mean age of 67 years. The mean (±SD) duration of these trials was 3.3 ± 0.59 years. Among older HRT initiators, cardiac death occurred in 293/12,278 (2.4%) compared with 274/11,989 (2.3%) in the control group with an OR of 1.04 [95% CI, 0.88–1.23]. No evidence of statistical heterogeneity was observed in the older initiator RCTs ($Chi^2 = 7.74$, $p = 0.46$, $I^2 = 0\%$). Among the younger HRT initiators, eight RCTs were identified with 10,775 participants with a mean age of 54.5 years. The mean (±SD) duration was 4.57 ± 1.62 years. In

Table 1
Baseline characteristics of the 32 included randomized controlled trials among women taking hormone replacement therapy (HRT) separated into younger versus older initiators. The baseline characteristics included are trial design, average follow-up time, number of participants, average age, dose of HRT, formulation of HRT and primary outcome.

Name, year	Design	Follow-up (years)	Number of participants (mean age in years ± standard deviation)	Dose and compound	Primary outcome
Early initiator RCTs					
Angerer, 2000	Observer-blind only	0.92 year	321 women (59.2 ± 4.2 years)	1 mg 17β-estradiol plus 0.025 mg gestodene for 12 days per month vs. 1 mg 17β-estradiol plus 0.025 mg gestodene for 12 days every 3rd month vs. control	The change of distensibility of the common carotid artery
Arrenbecht, 2002	Double-blind, placebo controlled	2 years	160 "healthy" women (53.5 ± 3.7 years)	50 μg/day or 100 μg/day of a 17β-estradiol transdermal patch vs. placebo	Lumbar spine bone mineral density
Fahlen, 2013	Open label	10.8 year	378 women with prior breast cancer (57.4 ± 5.3 years)	2 mg/day of estradiol valerate for women with a hysterectomy and 2 mg/day of estradiol for 21 days followed by 10 days of 10 mg/day of medroxyprogesterone vs. control	Breast cancer recurrence, cancer free survival
Giske, 2002	Double-blind, placebo controlled	2 years	166 women with prior hysterectomy (49.5 years)	0.5 mg mg/day of 17β-estradiol vs. 1 mg mg/day of 17β-estradiol vs. 2 mg mg/day of 17β-estradiol vs. placebo	Bone mineral density
Guidozzi, 1999	Open label	4 years	130 women with prior ovarian carcinoma, all participants under the age of 59, (mean age not provided)	0.625 mg/day of conjugated equine estrogen vs. control	Disease free interval and overall survival
Hall, 1994	Open label	2 years	200 women with rheumatoid arthritis (56 ± 5.5 years)	50 μg/day transdermal estradiol with oral norethisterone 1 mg for 12 days vs. calcium supplementation	Bone mineral density
Hall, 1998	Double-blind, placebo controlled	1 year	60 women with coronary artery disease (59.4 ± 6.6 years)	50 μg/day transdermal 17β-estradiol followed by 10 days of medroxyprogesterone acetate vs. oral 0.625 mg/day of conjugated estrogen with MPA vs. placebo	Angina pectoris and quality of life
Harman, 2014	Double-blind, placebo controlled	4 years	727 women (52.7 ± 2.6 years)	Either 0.45 mg/day of oral conjugated equine estrogen or 50 μg/day of transdermal 17β-estradiol each with 200 mg of oral progesterone for 12 days/month or placebo	Annual change in carotid intima media thickness and calcium artery score
Hoibraaten, 2000	Double-blind, placebo controlled	1.3 years	140 women (55.8 ± 6.5 years)	2 mg of estradiol plus 1 mg norethisterone acetate or placebo	Venous thromboembolism
Jirapinyo, 2003	Double-blind, placebo controlled	1 year	120 Thai women (54.3 ± 4.4 years)	2 mg/day of 17β-estradiol plus 1 mg/day norethisterone acetate vs. placebo	Lumbar and hip bone mineral density
Komulainen, 1999	Double-blind, placebo controlled	5 years	464 women (52.8 years)	2 mg/day of estradiol valerate plus 1 mg of cyproterone acetate or 300 IU/day of vitamin D plus 2 mg/day of estradiol valerate plus 1 mg of cyproterone acetate vs. 300 IU/day of vitamin D vs. placebo	Lumbar and femoral neck BMD
Kyllönen, 1998	Double-blind, placebo controlled	2 years	78 women (52.6 ± 1.5 years)	2 mg/day estradiol valerate with 10 mg/day of medroxyprogesterone acetate vs. placebo	Lumbar spine mobility
Manson, 2013	Double-blind, placebo controlled	5.6 years in the CEE plus MPA trial and 7.2 years in the CEE alone trial	8833 women, (55.1 years)	0.625 mg/day conjugated equine estrogen or 0.625 mg/day conjugated equine estrogen plus 10 mg/day medroxyprogesterone acetate vs. placebo	Coronary heart disease and breast cancer, global index which included stroke, pulmonary embolus, colorectal cancer, endometrial cancer, hip fracture, and death
Nachtigall, 1979	Double-blind, placebo controlled	10 years	168 chronically ill women (55 years)	2.5 mg/day of conjugated equine estrogen and 10 mg/day of medroxyprogesterone vs. placebo	Death, MI, carcinoma
Perez-Jaraiz, 1996	Open label	1 year	104 women (50 ± 5.5 years)	Transdermal 50 mg/day 17β-estradiol and medroxyprogesterone 10 mg/day for 12 days of the month vs. control	Bone mineral density

Samaras 1999	Open label	1 year	14 women with type II diabetes (57.5 ± 5.6 years)	2 months of conjugated equine estrogen 0.625 mg/day followed by 4 months of CEE plus medroxyprogesterone 5 mg daily vs. observation	Lipids, glycemic control, blood pressure, vascular distensibility and total and central abdominal adiposity
Schierbeck 2012	Open label	11 years	1006 women (49.7 ± 2.8 years)	2 mg/day of estradiol or 2 mg/day estradiol and or norethisterone acetate vs. control	Composite of death, admission to hospital for heart failure, myocardial infarction
Westendorp, 2000	Part open label, part double-blind placebo controlled	2 years	99 women (47.2 ± 4.1 years)	17β-estradiol and desogestrel vs. placebo or conjugated estrogen and norgestrel vs. control	Artery distensibility
Late initiator RCTs					
Binder, 2001	Double-blind, placebo controlled	0.75 year	59 sedentary women (82.3 ± 3.5 years)	0.625 mg/day conjugated estrogen plus 5 mg/day of tri-monthly medroxyprogesterone acetate for women with an intact uterus vs. placebo	Serum lipid and lipoprotein levels
Cherry, 2002	Double-blind, placebo controlled	2 years	1017 women with a prior myocardial infarction (62.6 ± 5.1 years)	2 mg/day estradiol valerate vs. Placebo	Cardiac death, nonfatal myocardial reinfarction, All-cause mortality
Clarke, 2002	Double-blind, placebo controlled	2.57 years	255 women with angiographically proven coronary artery atherosclerosis (66.6 ± 11.5 years)	2.5 mg/day of 17β-estradiol transdermal patch or 3 mg/day 17β-estradiol and 4 mg/day of norethisterone transdermal patch for those women with an intact uterus vs. placebo	Cardiac mortality, hospitalization for unstable angina, non-fatal myocardial infarction
Collins, 2006	Double-blind, placebo controlled	1 year	100 women with recent myocardial infarction (68.8 ± 8.8 years)	1 mg/day of 17β-estradiol and 0.5 mg/day of oral norethisterone acetate vs. placebo	Serum lipid profile, markers of coagulation and fibrinolysis
Gallagher, 2001	Double-blind, placebo controlled	3 years	489 women (71 ± 3.75 years)	0.625 mg/day of conjugated estrogens plus 2.5 mg/day of medroxyprogesterone for women with an intact uterus, 0.625 mg/day of conjugated estrogens for women with a hysterectomy vs. calcitriol vs. estrogen plus calcitriol vs. placebo	Change in bone mineral density over time
Herrington, 2000	Double-blind, placebo controlled	3.2 years	309 women with angiographically proven coronary artery atherosclerosis (65.8 ± 7.2 years)	0.625 mg/day of conjugated equine estrogen plus 2.5 mg/day of medroxyprogesterone acetate vs. placebo	Mean minimal coronary-artery diameter
Hodis, 2001	Double-blind, placebo controlled	2 years	222 women with no known CHD (62.2 ± 6.9 years)	1 mg/day of 17β-estradiol vs. placebo	Rate of change of carotid intima media thickness
Hodis, 2003	Double-blind, placebo controlled	3.3 year	226 with angiographically proven coronary artery stenosis (63.5 ± 6.4 years)	1 mg/day 17β-estradiol or 17β-estradiol plus medroxyprogesterone acetate vs. placebo	% change in coronary artery stenosis over the course of the study
Hodis, 2016	Double-blind, placebo controlled	5 years	643 women, average age (60.2 years)	1 mg/day of 17β-estradiol or 1 mg/day 17β-estradiol plus progesterone gel vs. Placebo	Rate of change of carotid intima-media thickness
Hulley, 1998	Double-blind, placebo controlled	4.1 years	2763 women with established coronary heart disease (66.7 ± 7 years)	0.625 mg/day of conjugated equine estrogen plus 2.5 mg/day of medroxyprogesterone acetate vs. placebo	Nonfatal myocardial infarction or coronary heart disease death
Maheux, 1994	Double-blind, placebo controlled	1 year	60 women (61 ± 1 years)	0.625 mg/day of conjugated estrogen vs. placebo	Skin thickness
Manson, 2013	Double-blind, placebo controlled	5.6 years in the CEE plus MPA trial and 7.2 years in the CEE alone trial	18,514 women, (67.3 years)	0.625 mg/day conjugated equine estrogen or 0.625 mg/day conjugated equine estrogen plus 10 mg/day medroxyprogesterone acetate vs. placebo	Coronary heart disease and breast cancer, global index which included stroke, pulmonary embolus, colorectal cancer, endometrial cancer, hip fracture, and death
Viscoli, 2001	Double-blind, placebo controlled	2.8 years	664 postmenopausal women who had a TIA or stroke within 90 days (71 ± 10 years)	1 mg/day of 17β-estradiol vs. placebo	Stroke, TIA
Waters, 2002	Double-blind, placebo controlled	2.8 years	423 women with known coronary artery stenosis (65 ± 9 years)	0.625 mg/day of conjugated equine estrogen (plus 2.5 mg/day of medroxyprogesterone acetate) hormone therapy vs. antioxidant vitamins vs. placebo	Change in minimum coronary artery lumen diameter

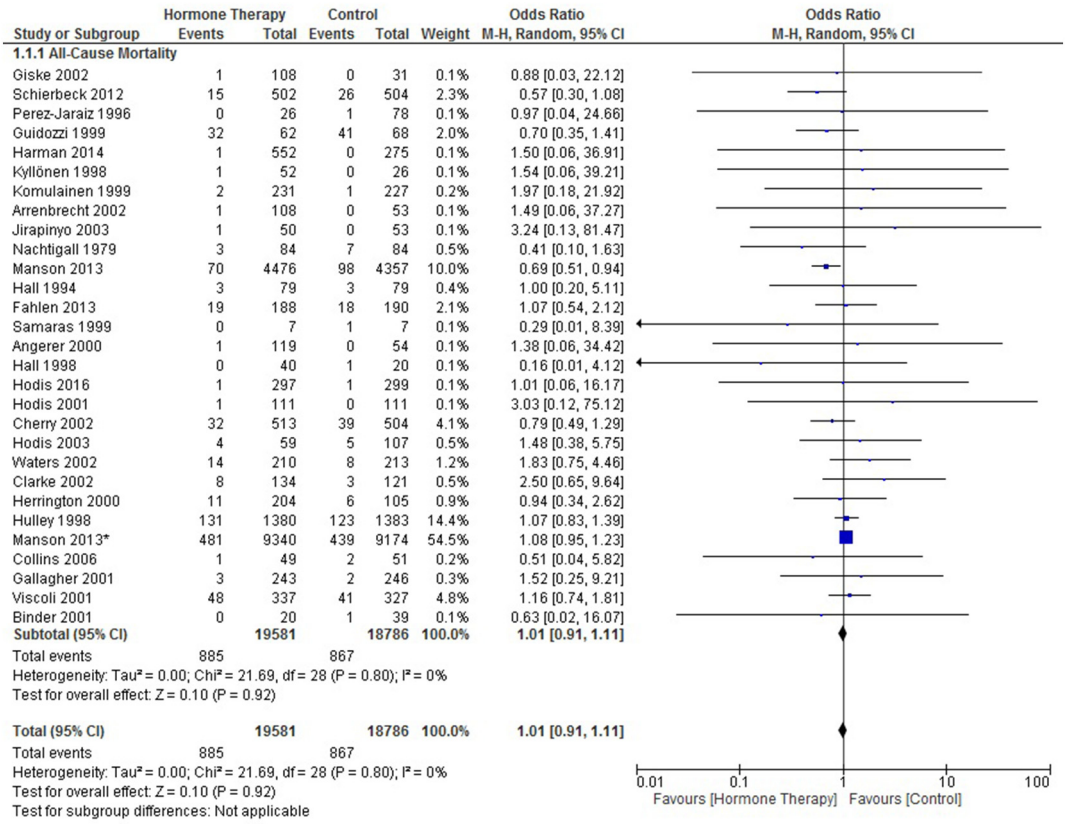

Fig. 2. Forrest plot for all-cause mortality. This forest plot represents the odd's ratio for hormone replacement therapy's effects on all-cause mortality for the included studies. The trials are listed in descending order based on average age of participants at trial baseline.

younger HRT initiators, cardiac death occurred in 26/5471 (0.5%) compared to 43/5304 (0.8%) in the control group with OR of 0.61 [95% CI, 0.37–1.00] (Fig. 3). There was no statistical heterogeneity noted among younger initiator trials (Chi = 6.42, $p = 0.49$, $I^2 = 0\%$). When performing the test for subgroup differences, there was significant heterogeneity noted between younger versus older initiators for cardiac death ($Chi^2 = 4.04$, $p = 0.04$, $I^2 = 75.2\%$). When excluding open-label trials [12,20,22], there was no heterogeneity observed between younger and older initiators of HRT and cardiac death ($Chi^2 = 0.86$, $p = 0.35$, $I^2 = 0\%$). The reduced risk of cardiac death in younger HRT initiators was not observed when excluding open label trials (OR 0.78 [95% CI, 0.44–1.40]). When excluding the WHI-HT trial there was heterogeneity observed between younger and older initiators and cardiac death ($Chi^2 = 4.56$, $p = 0.03$, $I^2 = 78.1$). When performing the fixed effect regression for cardiac death the intercept point estimate was −0.2 with a standard error of 0.11 ($p = 0.09$). For mean age, the point estimate was 0.003 with a standard error of 0.002 ($p = 0.1$). When using a random effects model for the regression analysis the intercept point estimate was −0.01 with a standard error of 0.4 ($p = 0.78$). For mean age the point estimate was 0.001 with a standard error of 0.007 ($p = 0.83$).

For the composite outcome of stroke, TIA, pulmonary embolism and DVT, eighteen RCTs [3,10,13,15,18,19,24–26,28–34,38] were identified with 36,844 participants. The average age was 63.0 years. The mean trial follow-up duration was 4.13 ± 0.67 years. The bias was judged to be low with 15 of 126 (12%) domains being labeled as high or questionable bias. One included RCT was open label [9]. The incidence of stroke, TIA, and systemic embolism in all HRT users was 1112/18,774 (5.9%) versus 734/18,070 (4.1%) in the control group, with OR of 1.52 [95% CI, 1.38–1.67]. Some evidence of heterogeneity that did not meet statistical significance was present (Chi = 25.80, $p = 0.08$, $I = 34\%$). In the older grouping, eleven RCTs were identified with 25,352 participants with a mean age of 66.9 years. The mean (±SD) follow-up duration was 3.44 ± 0.5 years. In the older HRT initiator grouping the incidence of stroke, TIA and systemic embolism in the treatment group was 942/12,818 (7.3%) versus 615/12,534 (4.9%) in non-users, with an OR of 1.52 [95% CI, 1.39–1.71]. Evidence of nonsignificant heterogeneity was present (Chi = 15.08, $p = 0.08$, $I = 34\%$). In the younger initiator grouping, seven RCTs were identified with 11,492 women with a mean age of 54.4 years. The mean follow-up duration was 5.73 ± 1.25 years. The incidence of stroke, TIA and systemic embolism among younger HRT initiators was 170/5956 (2.9%) compared to 119/5536 (2.1%) in the control group, with an OR of 1.40 [95% CI, 1.10–1.78]. There was no evidence of statistical heterogeneity among younger HRT initiator trials (Chi = 10.05, $p = 0.12$, $I = 40\%$) (eFigure 2). When performing the test for subgroup differences, there was no evidence of heterogeneity between younger and older initiators of HRT for the risk of stroke, TIA, and systemic embolism (Chi = 0.52, $p = 0.47$, $I = 0\%$). When excluding Schierbeck et al. [10], the only open label RCT which reported a stroke, TIA or systemic embolism outcome, there was still no heterogeneity found between younger and older initiators of HRT ($Chi^2 = 0.06$, $p = 0.81$, $I^2 = 0\%$). When performing the fixed effect regression for stroke, TIA or systemic embolism the intercept point estimate was −0.3 with a standard error of 0.11 ($p = 0.006$). For mean age, the point estimate was 0.006 with a standard error of 0.002 ($p = 0.0003$). When using a random effects model for the regression analysis the intercept point estimate was −0.19 with a standard error of 1.5 ($p = 0.899$). For mean age the point estimate was 0.0014 with a standard error of 0.0251 ($p = 0.96$).

4. Discussion

This is the first meta-analysis we are aware of that tests the timing hypothesis in a prespecified manner in regard to mortality, CHD, stroke, TIA, and venous thromboembolism and its results are consistent with reduced all-cause mortality when HRT is used in younger women

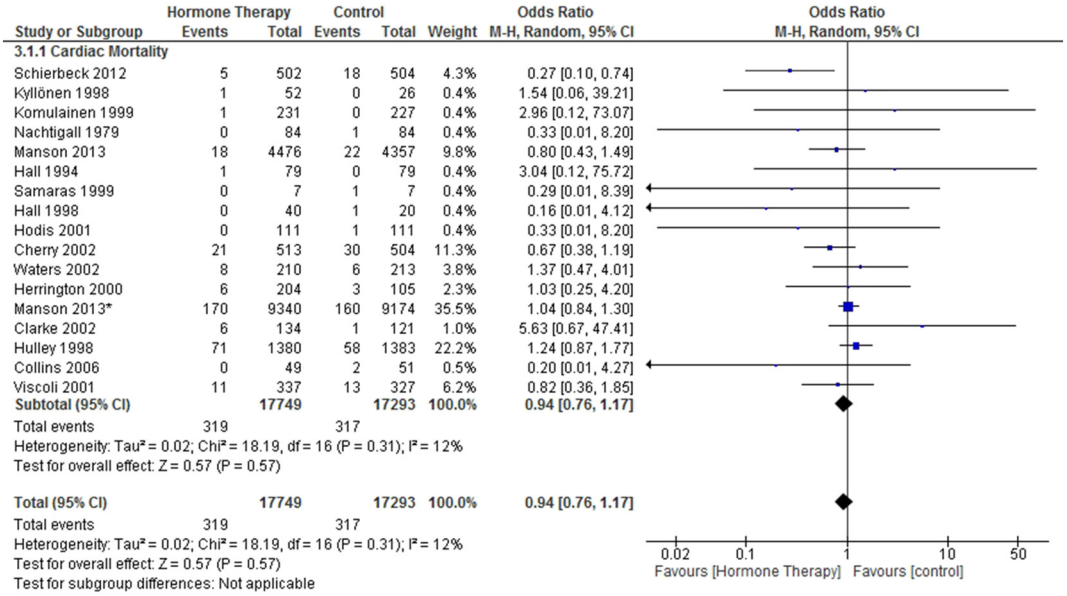

Fig. 3. Forest plot for cardiac mortality. This forest plot represents the odd's ratio for hormone replacement therapy effect's on cardiac death for the included studies. The trials are listed in descending order based on average age of participants at trial baseline.

with a number needed to treat (NNT) of 100. The NNT for cardiac mortality was 333 in younger menopausal women. However, these findings should be viewed with caution since exclusion of open label trials, erased the cardiac mortality benefit. Once explanation is that this analysis was based on fewer events and could have been unpowered to detect differences. Furthermore, the composite outcome of stroke, TIA, and systemic embolism was increased all HRT users with no difference between the subgroups. The meta-regression suggested that as age increases HRT has worse effects on stroke, TIA, and systemic embolism. There still remains risk when younger women take HRT and this risk most likely increases with age. HRT was found to have a number needed to harm (NNH) of 56 for this outcome.

A prior meta-analysis of 43 RCTs with a mean trial duration of 4.6 years found no difference in all-cause mortality or disease specific mortality including cardiac, stroke, or cancer mortality between HRT users and nonusers [39]. However, in a subgroup analysis of five RCTs, all-cause mortality was decreased in younger women randomized to HRT (RR 0.70 [95% CI, 0.52–0.95]). Given the multifaceted effects HRT has on various pathophysiologic mechanisms and diseases, including CVD, stroke, and venous thromboembolism, all-cause mortality provide an important clinically significant representation of HRT's total risks and benefits. This subgroup difference based on average age at randomization has been observed in an older, prior fixed effects meta-analyses however, statistical heterogeneity was not analyzed and a sensitivity analysis was not performed. A meta-analysis completed by Salpeter et al. [40] analyzed a composite outcome of CHD events defined as nonfatal MI and cardiac death in 23 RCTs stratified by average age of participants at the start of the clinical trial. They found that younger women taking HRT had a decreased risk of CHD events (OR 0.68 [95% CI, 0.48–0.96]) when compared to older women (OR 1.03 [95% CI, 0.91–1.16]). However, a fixed effects model was not the most appropriate model given the wider variation between individual RCTs and biased the results in favor of HRT. In our meta-analysis, we used a random effects model and HRT in younger initiators trended toward reduction in CHD events but did not meet statistical significance. Furthermore, when we excluded open-label RCTs the reduction in CHD events was not observed. Interestingly, there was no difference in the stroke, TIA and systemic embolism risk between younger and older initiators of HRT with a number needed to harm (NNH) of 56. However, the meta-regression analysis performed suggested increased risk of this composite outcome with increasing age.

The average follow-up of RCTs which reported an all-cause mortality was 3.8 years. The safe HRT duration is less clear. The 2017 statement from the North American Menopause Society on HRT stresses shared decision making when determining duration of HRT for the treatment of vasomotor symptoms [41]. A recent analysis from the WHI, reported mortality outcomes from both the intervention and postintervention phases of their HT clinical trial. This included 18 years of total follow-up from their CEE alone trial and the CEE plus MPA trial. In the pooled analysis of all HRT users no difference in all-cause mortality (27.1% in the HRT group vs. 27.6% in the placebo group); hazard ratio [HR], 0.99 [95% CI, 0.94–1.03] was seen. The cardiac death rate was 8.9% for HRT users vs. 9.0% in the placebo group (HR, 1.00 [95% CI, 0.92–1.08]). During the intervention phase of the WHI-HT clinical trial, a post-hoc analysis of women aged 50–59 years, found that all-cause mortality was reduced with HRT users (HR, 0.87 [95% CI, 0.43–0.87]). The all-cause mortality endpoint in this subgroup trended toward reduction at 18 years from trial baseline, however, it failed to meet statistical significance (HR, 0.61 [95% CI, 0.76–1.00]) [42].

There are limitations when performing a meta-analysis of this kind. Few trials included studied the endpoints of this meta-analysis (all-cause mortality, cardiac morality, CHD events and stroke, TIA and systemic embolism) in a pre-specified manner. Therefore, it likely that these outcomes were self-reported by participants and not identified through standardized or rigorous adjudication methods thus subjecting them to significant bias (including recall and reporting bias). In these trials, it is also unknown if events of interest occurred in study participants which were not reported to the study investigators or reported in the RCT's published manuscript. Furthermore, our groupings of younger and older initiators were determined based on the average of participants at trial baseline and for the majority of included RCTs we were unable to obtain age-specific subgroup data. A more accurate way of determining younger and older HRT initiators would be to group trials based on time since the onset of menopause (regardless of what age menopause occurred). Another major limitation is the wide variability in the medication formulation and route of HRT administration. In this meta-analysis, all formulations of systemic HRT studied were pooled and studied as HRT. The outcomes of interest may be affected by formulation and route of delivery. In addition, this meta-analysis included RCTs which were open label, introducing potential bias to the overall conclusions of the study. The largest RCT included with the most events of interest is the WHI trial. The early termination of the WHI-HT trials

could have led to less reliable results for the primary endpoints of this meta-analysis, especially since this large trial contributes the most weight. Furthermore, the variability in follow-up times for each RCT was no controlled for in the analysis (Table 1). For these reasons, this analysis is unable to comment on the effect HRT duration on each endpoint.

The benefits of HRT on all-cause mortality and cardiac death may be related to the timing of initiation following the onset of menopause as the 'timing hypothesis' states. In this systematic review and meta-analysis, HRT use was found to reduce all-cause mortality and cardiac mortality in younger HRT initiators but not in older initiators and significant heterogeneity of treatment effect was found between these groups in terms of CHD events. However, this analysis has important limitations and the findings should be viewed with caution as the reduction in cardiac mortality was eliminated when excluding open-label trials. Furthermore, HRT use was found to confer an increased risk of stroke, TIA and systemic embolism in all users and this risk appeared to increase as average age increased. Further research is needed to better understand HRT's effects when initiated soon after the onset of menopause.

Conflict of interest disclosure

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.01.001.

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