# Effects of Low-Dose Versus Placebo or Conventional-Dose Postmenopausal Hormone Therapy on Variables Related to Cardiovascular Risk: A Systematic Review and Meta-Analyses of Randomized Clinical Trials

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**Context:** Hormone therapy (HT), the most efficient treatment for menopausal symptoms, might have deleterious cardiovascular (CV) effects.

**Objective:** This study aimed to evaluate the effects of low-dose estrogen HT on CV risk factors vs conventional-dose HT and placebo in postmenopausal women with no established CV disease.

**Data Sources:** MEDLINE, Cochrane Central, and EMBASE were searched for trials published in 1990–2013; a hand search of reference lists of selected articles was performed; and ClinicalTrials.gov was searched for unpublished trials.

**Study Selection:** Within randomized controlled trials of healthy postmenopausal women comparing low-dose HT to placebo or conventional-dose HT, 11 418 studies were initially identified.

**Data Extraction:** Data were independently extracted by two investigators. Disagreements were resolved by a third author.

**Data Synthesis:** Twenty-eight trials (3360 patients) were included. Low-dose HT vs placebo or conventional-dose HT did not effect weight, body mass index (BMI), blood pressure, C-reactive protein, or high-density lipoprotein cholesterol (HDL-C). Low-dose HT was associated with lower levels of total cholesterol (−12.16 mg/dL, 95% confidence interval [CI], −17.41–−6.92) and low-density lipoprotein cholesterol (LDL-C) (−12.16 mg/dL; 95% CI, −16.55–−7.77) vs placebo. Compared with conventional-dose HT, low-dose HT was associated with higher total cholesterol (5.05 mg/dL; 95% CI, 0.88–9.21) and LDL-C (4.49 mg/dL; 95% CI, 0.59–8.39). Low-dose HT was not associated with differences in triglycerides vs placebo. Oral, low-dose HT was associated with lower triglycerides vs conventional-dose HT (−14.09 mg/dL; 95% CI, −24.2–−3.93).

**Conclusion:** In this population of apparently healthy postmenopausal women, the effect of low-dose HT did not differ from that of placebo or conventional-dose HT regarding weight, BMI, blood pressure, CRP, or HDL-C. In contrast, low-dose HT was associated with better lipid profile vs placebo, and induced higher total and LDL-C and lower triglycerides vs conventional-dose HT. **(*J Clin Endocrinol Metab* 100: 1028–1037, 2015)**

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Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HT. hormone therapy; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PEPI, Postmenopausal Estrogen/Progestin Interventions; RCT, randomized clinical trial; TC, total cholesterol; WHI, Women's Health Initiative.

Hormone therapy (HT) is the most efficient treatment for menopausal symptoms such as hot flashes, which affect 75% of women older than 50 years of age (1). However, the effects of HT on cardiovascular (CV) risk remain controversial (2). The publication of the Women's Health Initiative (WHI) study in 2002 drew attention to a possible increase in the prevalence of CV events in postmenopausal women using HT (3). The WHI study reported a significant increase in myocardial infarction (MI), venous thromboembolism, and stroke in postmenopausal women receiving HT compared with those receiving placebo (3, 4), contradicting the findings of previous observational studies (5, 6), which had indicated a cardioprotective effect of HT in this population. A detailed analysis of the WHI study highlighted the negative effect of factors such as aging (7), presence of CV risk factors (8, 9), and years since menopause (10) on CV events. It also suggested the need for further clinical trials to test lower HT doses and alternative routes of administration (11–13).

Conventional estrogen doses may produce supraphysiological plasma concentrations of estrogen in postmenopausal women, leading to CV risk (14) and harm associated with disturbances in thrombogenesis and vascular remodeling (15). Lower HT doses seem to be related to lower risk of venous thromboembolism (16–18) and stroke (19). However, randomized clinical trials comparing CV risk associated with conventional vs lower-dose HT are not yet available (20), and dose-dependent effects of HT on variables related to CV risk have only been studied in small clinical trials (11, 21–25).

For a better understanding of the effects of low-dose HT on CV risk, we conducted a systematic review with meta-analysis of pooled data from randomized clinical trials (RCTs) reporting on variables related to CV risk (weight, body mass index [BMI], blood pressure [BP], C-reactive protein [CRP], and lipids) in postmenopausal women with no evidence of CV disease.

## Materials and Methods

This systematic review with meta-analysis was performed in accordance with Cochrane Collaboration guidelines (26) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (26).

### Eligibility criteria and trial selection

We gathered data from RCTs designed to assess the effects of low-dose HT on variables related to CV risk in postmenopausal women. Studies were included if they 1) were RCTs of healthy postmenopausal women, comparing low-dose HT to placebo or conventional-dose HT; 2) included at least 15 patients in each group of interest; 3) provided extractable data on at least one CV variables, namely BP, BMI, weight, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, CRP; and 4) were published in English.

Conventional-dose HT was defined as at least 0.625 mg conjugated equine estrogen and equipotent doses of other formulations: 2 mg estradiol valerate or oral 17$\beta$-estradiol, 150 $\mu$g percutaneous 17$\beta$-estradiol gel, 50 $\mu$g 17$\beta$-estradiol patches, or 300 $\mu$g intranasal estradiol (3, 10, 11, 15, 27). All formulations employing lower doses than those classified as conventional were defined as low dose ($\leq$0.3 mg conjugated equine estrogen, $\leq$1 mg estradiol valerate or oral 17$\beta$-estradiol, $\leq$100 $\mu$g percutaneous 17$\beta$-estradiol gel, l50 $\mu$g 17$\beta$-estradiol patches, or $<$300 $\mu$g intranasal estradiol).

For studies with multiple doses, we defined as experimental the group receiving the lowest dose of estrogen associated with the lowest dose of progesterone. The control group was defined as placebo or conventional-dose HT. Groups receiving intermediate doses were not included in the analyses. Similarly, studies with low-dose estrogen but without placebo or conventional doses for comparison were excluded from the analyses.

For multiple articles on the same sample, the article containing the most complete information was chosen. For crossover studies, the entire treatment period was included if the study clearly described the absence of carry-over effects in the statistical analysis; or, if the study did not describe this analysis, only the results of the first period of treatment were considered.

Eligibility assessment was performed independently in an unblended, standardized manner by two reviewers (G.C. and R.B.R.). Inconsistencies between these two reviewers were settled by a third reviewer (P.M.S.).

### Search strategy

MEDLINE (accessed through PubMed), Cochrane Central Register of Controlled Trials (Cochrane CENTRAL accessed through Wiley Science) and EMBASE were searched comprehensively to identify RCTs published between January 1990 and August 2013. The last search was run in August 2013. The search strategy is available as Supplemental Materials and Methods.

We also searched http://ClinicalTrials.gov to retrieve RCTs with unpublished results. Finally, we searched the references of published studies, and relevant reviews and meta-analyses regarding the role of HT in postmenopausal women were examined to identify additional studies for inclusion.

### Data extraction

Titles and abstracts of all articles retrieved were independently evaluated by two investigators, and full-text evaluation was performed when necessary. G.C. and R.B.R. evaluated and selected these articles for inclusion in the analyses. Disagreements were resolved by consensus or by consultation to a third reviewer (P.M.S.). If the required data were not located in the published article, authors were contacted to provide the missing information.

The data collected included: first author and study group, publication year, journal, number of patients, mean age, time since menopause (when possible), pre-existing disease, medications, country, predominant race of participants, number of participants, intervention regimens, type of control (placebo or no treatment), duration of followup, and values of the variables of interest (weight, BMI, BP, CRP, and lipids).

### Assessment of risk of bias

The quality of trials was independently assessed by two reviewers following the Cochrane Handbook for Systematic Reviews of

Interventions (26) on the basis of adequate random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and intention to treat analysis.

To assess publication bias, funnel plots were created and analyzed by visual inspection.

### Data analysis

Individual studies evaluated the variables of interest before and after treatment in each arm. However, because most studies did not provide information on SDs for pre- and post-treatment variables, pooled-effect estimates were obtained using after-treatment measurements only.

Results were presented as mean differences between treatment arms with 95% confidence intervals (CIs). Calculations were performed using a random effects model because the studies were not sufficiently similar to warrant the use of a fixed-effects model. $P < .05$ was considered statistically significant. Heterogeneity was assessed using $I^2$-test and Cochrane Q statistics. $I^2$ greater than 25% indicated moderate heterogeneity and $I^2$ greater than 50% indicated substantial heterogeneity. All analyses were conducted using Review Manager 5.2 (Cochrane Collaboration).

Meta-analyses were performed for two subgroups: low-dose HT compared with placebo, and low-dose HT compared with conventional dose. Each analysis was considered a subgroup. Differences between subgroups were tested considering a significance of $P < .05$. Overall effects were informed only if subgroup comparisons were not statistically significant.

To overcome unit-of-analysis error in studies with multiple intervention groups (low-dose, placebo, and conventional dose), the low-dose group (shared group) was divided by two; this allowed two reasonably independent comparisons (low-dose compared with placebo and low-dose compared with conventional dose).

Sensitivity analysis was performed as prespecified: route of administration (oral or nonoral estrogen HT) and type of HT (unopposed estrogen or combined [estrogen-progestin] HT). Nonoral low-dose HT subgroup analysis was not performed because only two studies were available.

To evaluate whether the use of deltas instead of after-treatment measurements would substantially affect the conclusions, we repeated the analysis using deltas as the outcome for each arm. For those analyses, we had to input SD values for the changes, because in most of the studies they were missing. The imputations were performed using three different values for the before-after correlation coefficients: mean coefficient for studies providing sufficient information, 0.5 (low correlation), and 0.99 (high correlation). The conclusions were similar for all the analyses.

## Results

### Description of studies

The search yielded 11 418 studies, of which 75 were retrieved for detailed analysis (Figure 1). Twenty-eight trials met the eligibility criteria and were included in the meta-analyses (Table 1) (11, 21, 22, 24, 28–50). All these studies had obtained approval from ethics committees.

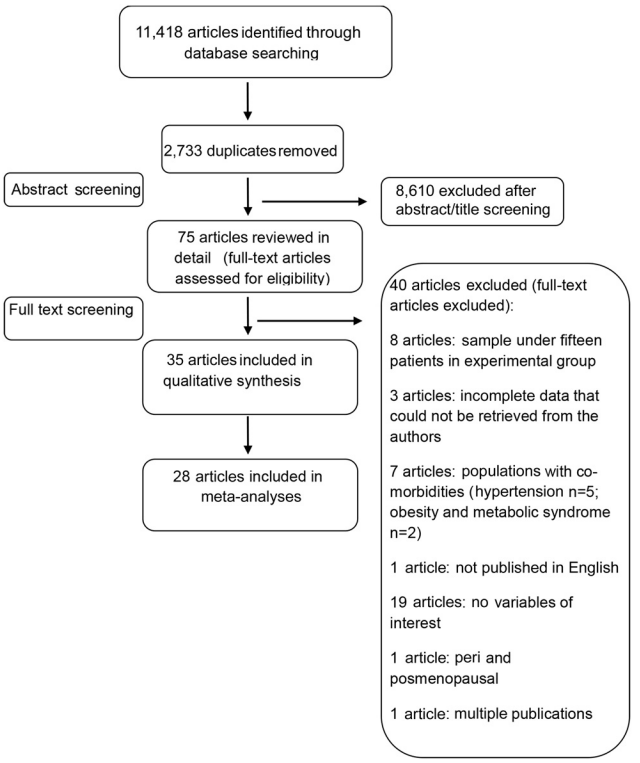


**Figure 1.** Flow diagram of the literature search and trials selection process.

Mean trial duration was 11.3 months (range, 2–26 mo) and the mean age of participants (± SD) at baseline was 54.7 ± 3.1 years.

Seven articles with low-dose HT were included in the discussion, but not in the meta-analyses. Six articles only evaluated low-dose therapy (no placebo or conventional dose for comparison) (51–56), one (57) did not provide sufficient information for inclusion in the meta-analysis, and two had incomplete data on one or more of the variables of interest and were not available from the authors (24, 46).

### Methodological quality and risk of bias

Random allocation of treatment was performed in 24 studies (11, 21, 22, 24, 28, 29, 31–37, 40–48, 50, 58). Allocation concealment methods were reported in 14 studies (11, 22, 31–37, 41, 42, 44, 47, 50). Thirteen trials were double blinded (11, 21, 22, 24, 28, 31, 34, 36, 40, 41, 43, 44, 47).

Figure 2 summarizes the risk of bias for the 28 studies included in meta-analyses. Funnel plots are shown as Supplemental Figures 1–7).

### Quantitative data synthesis: Effects of low-dose HT

#### *Weight*

Data were available from four trials totaling 650 postmenopausal women. One study evaluated low-dose HT vs

**Table 1.** Characteristics of Studies Included in the Meta-analyses

| Study | No. | Mean Age, Years | Intervention Groups | Control | Followup, Months | Evaluated Outcomes |
|---|---|---|---|---|---|---|
| Alexandersen et al (28) | 301 | 57.9 ± 3.8 | 1 mg 17 β estradiol + 0.5 mg NETA[a]; levormeloxifene 1,25;5;10;20 mg | Placebo | 13 | TC, HDL-C, LDL-C |
| Angerer et al (PHOREA) (29) | 197 | 58.3 ± 4.5 | 1 mg 17 β estradiol + 25 mcg gestodene 14d/m[a]; 1 mg 17 β estradiol + 25 mcg gestodene 14days each three months | Placebo | 12 | BMI, BP |
| Bingol et al (30) | 78 | 52.6 ± 4.9 | 1 mg 17 β estradiol + 0.5 NETA | Placebo | 6 | BMI, weight, BP, CRP, TC, HDL-C, LDL-C, TG |
| Brynhidsen et al (31) | 266 | 55.2 ± 4.8 | 0.025 mg 17 β estradiol TD + 0.125 mg NETA | Placebo | 12 | TC, HDL-C, LDL-C, TG |
| Casanova et al (32) | 40 | 51 ± 2.7 | 1 mg 17 β estradiol + 2 mg drospirenone; 300 mcg 17 β estradiol intranasal + 200 mg micronized progesterone 14d/m | | 4 | BMI, BP, CRP, TC, HDL-C, LDL-C, TG |
| Davidson et al (33) | 264 | 58.1 ± 5.8 | 1 mg 17 β estradiol;1 mg 17 β estradiol + 0.25 mg noretindrone acetate[a]; 1 mg 17 β estradiol + 0.5 mg noretindrone acetate | Placebo | 6 | TC, HDL-C, LDL-C, TG |
| Kraker et al (34) | 362 | 55 ± 5.1 | 1 mg 17 β estradiol + 5 mg dydrogesterone;0.625 EEC + 5 mg AMP | | 13 | TC, HDL-C, LDL-C, TG |
| Gambacciani et al (35) | 70 | 52.7 ± 0.5 | 1 mg 17 β estradiol + 2 mg drospirenone | 1000 mg calcium | 3 | BP |
| Hemelaar et al (36) | 152 | 54.4 ± 4.3 | 50 mcg 17 β estradiol TD; 1 mg 17 β estradiol; 1 mg 17b estradiol + 25 mcg gestodene[a] | Placebo | 13 | TC, HDL-C, LDL-C, TG |
| Hwanget al (EPAT) (37) | 222 | 60.8 ± 6.6 | 1 mg 17 β estradiol | Placebo | 6 | TC, HDL-C, LDL-C, TG |
| Ichikawa et al (38) | 38 | 55.1 ± 6.9 | 36 mcg 17 β estradiol TD + 2.5 mg AMP 12d/m; 0.625 mg CEE + 5 mg AMP 12d/m | | 12 | BP |
| Kaya et al (39) | 80 | 50.8 ± 3.5 | 1 mg 17 β estradiol + 10 mg dydrogesterone 14d/m | Placebo | 12 | BP |
| Koh et al (40) | 57 | 57 ± 1 | 0.625 mg EEC + 100 mg micronized progesterone; 0.3 mg EEC + 100 mg micronized progesterone | | 2 | CRP, TC, HDL-C, LDL-C, TG |
| Lacut et al (41) | 196 | 43–70 | 1 mg 17β estradiol + 100 mg micronized progesterone; 50 mcg 17 β estradiol TD + 100 mg micronized progesterone 14 d/m | Placebo | 6 | CRP |
| Lobo et al (HOPE) (11) | 749 | 51.6 ± 3.7 | 0.625 mg EEC;0.625 mg EEC + 2.5 AMP; 0.45 mg EEC; 0.45 mg EEC + 2.5 mg AMP; 0.45 mg EEC + 1.5 mg AMP; 0.3mgEEC + 1.5 mg AMP[a]; 0.3 EEC | Placebo | 24 | TC, HDL-C, LDL-C, TG |
| Loh et al (21) | 96 | 53.9 ± 7.6 | 1 mg 17β estradiol + 0.5 mg NETA; 2 mg 17 β estradiol + 1 mg NETA | | 6 | TC, HDL-C, LDL-C |
| Odabasi et al (42) | 120 | 50.5 ± 2.7 | 1 mg 17 β estradiol + 0.5 mg NETA 2 mg 17 β estradiol + 1 mg NETA | | 6 | BMI, weight |
| Samsioe et al (43) | 120 | 56 | 1 mg 17β estradiol + 0.25 mg NETA[a] 1 mg 17b estradiol + 0.5 mg NETA | Placebo | 12 | TC, HDL-C, LDL-C, TG |
| Steiner et al (44) | 222 | 61 | 1 mg 17β estradiol | Placebo | 24 | BP |
| Stevenson et al (24) | 579 | 56.4 ± 4.7 | 1 mg 17β estradiol + 5 mg dydrogesterone 14d/m[a];1 mg 17β estradiol + 10 mg dydrogesterone 14d/m; 2 mg 17β estradiol + 10 mg dydrogesterone 14d/m; 2 mg 17β estradiol + 20 mg dydrogesterone 14d/m | Placebo | 26 | HDL-C (TC, LDL-C and TG included in systematic review) |
| Stork et al (PHOREA) (45) | 203 | 60.2 ± 4.3 | 1 mg of 17β estradiol + 25 mcg gestodene 12d/m[a]; 1 mg of 17β estradiol + 25 mcg gestodene12d/m each three months | Placebo | 12 | CRP, TC, HDL-C, LDL-C, TG |
| Tankó et al (46) | 240 | 58 ± 4 | 1 mg 17β estradiol + 1 mg drosperinone[a]; 1 mg 17β estradiol + 2 mg drosperinone; 1 mg 17β estradiol + 3 mg drosperinone | Placebo | 24 | BP |
| Thorneycroft et al (HOPE) (47) | 822 | 51.6 ± 3.7 | 0.625 mg CEE; 0.625 mg CEE + 2.5 AMP; 0.45 mg CEE;0.45 mg CEE + 2.5 mg AMP; 0.45 mg CEE + 1.5 mg AMP; 0.3 mg CEE + 1.5 mg AMP[a]; 0.3 mg CEE | Placebo | 24 | Weight |
| Tugrul et al (48) | 246 | 51.2 ± 2.6 | 0.625 mg CEE + 2.5 AMP; 1 mg 17β estradiol + 0.5 mg NETA | | 12 | Weight, TC, HDL-C, LDL-C, TG |
| Van Baal et al (22) | 30 | 52 ± 3 | 1 mg 17β estradiol + 5 mg dydrogesterone[a]; 1 mg 17β estradiol + 10 mg dydrogesterone | Placebo | 15 | CRP |
| Villa et al (49) | 48 | 53.4 ± 3.6 | 1 mg 17β estradiol; 2 mg 17β estradiol | Calcium 500 mg | 3 | BMI |
| Villa et al (58) | 40 | 52 ± 3.3 | 1 mg of 17β estradiol + 2 mg drospirenone | Placebo | 6 | BP, TC, HDL-C, LDL-C, TG |
| Wakatsuki et al (50) | 45 | 53.4 ± 7.3 | 0.625 mg CEE; 0.3125 CEE | Placebo | 3 | CRP, TC, HDL-C, LDL-C, TG |

Abbreviations: AMP, medroxyprogesterone acetate; CEE, conjugated equine estrogen; CRP = c-reactive protein; d/m, days per month; NETA, norethisterone acetate; TD, transdermal; TG, triglycerides.

[a] Treatment at a low-dose selected for meta-analyses (for studies with multiple low-dose HT).

placebo (30). Two studies compared low-dose and conventional-dose HT (42, 48). One study (47) had three arms. All studies employed estrogen-progestin.

Compared with placebo (−1.36 kg; 95% CI, −3.60–0.87) (Figure 3) or conventional-dose HT (−1.44 kg; 95% CI, −3.15–0.28) (Figure 4), low-dose HT was not associated with changes in weight. The test for subgroup differences was not significant ($P = .96$).

## BMI

Data from five trials were available totaling 375 postmenopausal women. All used oral, low-dose HT. Two studies evaluated low-dose HT vs placebo (29, 30). Two studies involved low-dose and conventional-dose HT (32, 42). One study (49) had three arms. Unopposed estrogen was used in one study (49). Low-dose HT was not associated with changes in BMI when compared with placebo (−0.09 kg/m$^2$; 95% CI, −0.95–0.77) (Figure 3) or conventional-dose HT (0.45 kg/m$^2$; 95% CI, −0.38–1.28) (Figure 4). Sensitivity analysis of combined estrogen-progestin low-dose HT did reveal difference in the following: combined low-dose HT vs placebo (−0.19 kg/m$^2$; 95% CI, −1.08–0.69; $P = .67$); combined low-dose HT vs conventional-dose HT (0.46 kg/m$^2$; 95% CI, −0.39–1.31; $P = .29$) (data not shown).

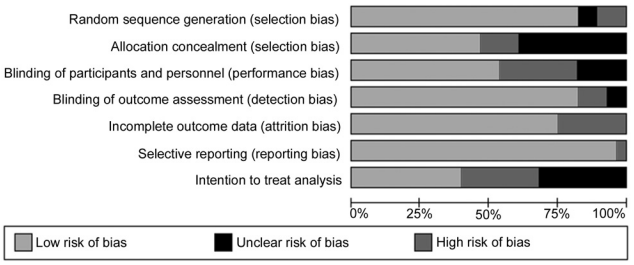


**Figure 2.** Risk of bias summary of included studies.

## BP

Data were available from nine trials including 843 postmenopausal women. Seven trials evaluated low-dose HT vs placebo (29, 30, 35, 39, 44, 46, 58). Two studies evaluated low-dose and conventional-dose HT (32, 38). Unopposed estrogen was used in only one study (44). Overall, low-dose HT did not reach a statistically significant effect on BP (Figures 3 and 4). There were no substantial changes in the results when the one study with unopposed estrogen (43) was removed from the analysis (data not shown).

## CRP

Data were available from seven trials totaling 614 postmenopausal women. Three studies evaluated low-dose HT vs placebo (22, 30, 45). Two studies compared low-dose with conventional-dose HT (32, 40), and two studies (41, 50) had three arms. Unopposed estrogen was used in only one study (50).

When compared with placebo, low-dose HT was associated with nonsignificant differences in CRP (0.36 mg/L; 95% CI, −0.14–0.86) (Figure 3). No changes were observed when low-dose HT was compared with conventional-dose HT (−0.35 mg/L; 95% CI, −0.94–0.24) (Figure 4). Two studies employed transdermal agents in the control group (32, 41). Sensitivity analysis of low-dose oral vs conventional oral HT revealed a trend to increased CRP with conventional oral doses (−0.67 mg/L; 95% CI, −1.42–0.09, $P = .07$, data not shown). In the comparison of combined estrogen-progestin low-dose HT vs placebo, combined low-dose HT was not associated with substantial changes in CRP (−0.11 mg/L; 95% CI, −0.71–0.49; $I^2$, 0%, data not shown).

## Lipids

Data from 17 trials were available for TC (n = 2321) and LDL-C (n = 2323), 18 for HDL-C (n = 2499), and 15 for triglycerides (n = 2127). Nine studies evaluated low-dose HT vs placebo (11, 28, 30, 31, 33, 36, 37, 43, 45, 58). Five studies compared low-dose HT with conventional-dose HT (21, 32, 34, 40, 48). Four studies had three arms (11, 24, 49, 50).

Three studies were performed with unopposed estrogen (37, 49, 50). Two studies employed nonoral HT in the low-dose group (31) and in the conventional-dose group (32).

## TC

TC was lower with low-dose HT than with placebo (−12.16 mg/dL; 95% CI, −17.41–−6.92) (Figure 3). Conversely, the low-dose HT group had higher levels of TC (5.05 mg/dL; 95% CI, 0.88–9.21) in comparison with conventional-dose HT (Figure 4). Similar results were obtained with sensitivity analysis of combined estrogen-progestin HT (low-dose estrogen–progestin HT vs placebo, −12.21 mg/dL; 95% CI, −17.83–−6.60; $P < .001$; low-dose estrogen–progestin HT vs conventional dose, 5.1 mg/dL; 95% CI, 0.96–9.42; $P = .02$) (data not shown) and low-dose oral agents (vs placebo, −11.30 mg/dL; 95% CI, −16.94–−5.67; $P < .001$; vs conventional dose, 5.4 mg/dL; 95% CI, 1.10–9.83; $P = .02$) (data not shown). Significant heterogeneity was verified for TC vs placebo. Sensitivity analyses did not reveal heterogeneity in this subgroup.

## LDL-C

When compared with placebo, the low-dose HT group had lower LDL-C (−12.16 mg/dL; 95% CI, −16.55–−7.77) (Figure 3). Conversely, a significant increase in LDL-C was observed in the low-dose vs conventional-dose group (4.49 mg/dL; 95% CI, 0.59–8.39) (Figure 4). Sensitivity analysis of low-dose estrogen–progestin HT was not associated with substantial changes (low-dose estrogen–progestin HT vs placebo, −11.8 mg/dL; 95% CI, −15.57–−8.1; $P < .001$; low-dose estrogen–progestin HT vs conventional dose, 4.4 mg/dL; 95% CI, 0.45–8.37; $P = .03$) (data not shown). Oral low-dose agents also produced similar results (vs placebo, −11.6 mg/dL; 95% CI, −15.5–−7.6; $P < .001$; vs conventional dose, 5.18 mg/dL; 95% CI, 1.04–9.3; $P < .001$) (data not shown).

## HDL-C

The effects of low-dose HT on HDL-C were not significantly different from those of placebo (1.42 mg/dL; 95% CI, −2.75–5.58) (Figure 3) or conventional-dose HT (1.01 mg/dL; 95% CI, −2.32–4.33) (Figure 4). Sensitivity analysis of low-dose estrogen–progestin HT did not reveal differences regarding HDL-C (vs placebo, 1.64 mg/dL; 95% CI, −3.4–6.7; vs conventional dose, 1.2 mg/dL; 95% CI, −2.6–5.0) (data not shown). Similar results were obtained for oral low-dose HT agents (vs placebo, 1.4 mg/dL; 95% CI, −3.2–6.0; vs conventional dose, 1.4 mg/dL; 95% CI, −2.2–5.0). Sensitivity analysis did not explain the heterogeneity observed.

Because of the high heterogeneity observed for HDL-C, additional analyses were conducted. After removal of

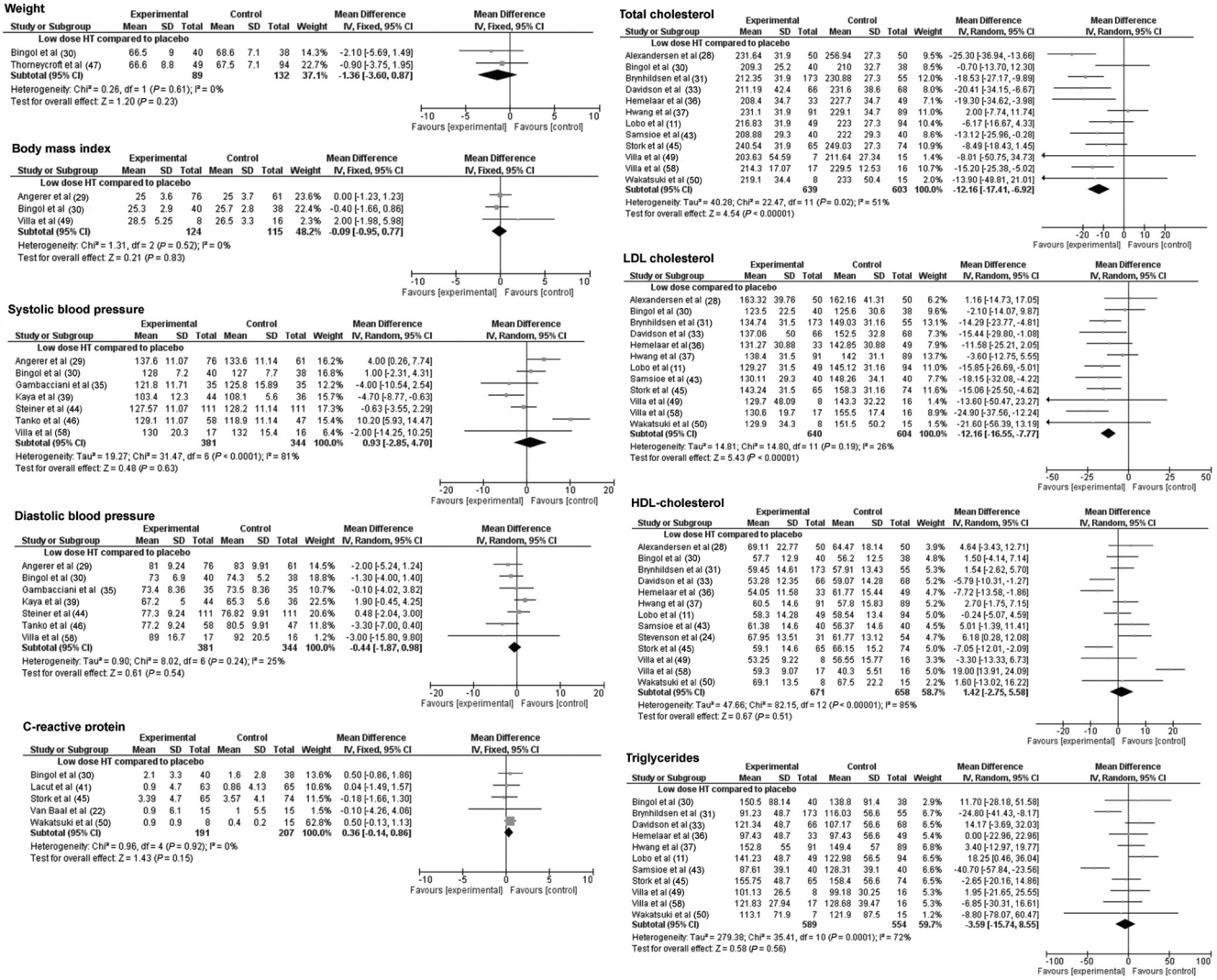


**Figure 3.** Effects of low-dose HT compared with placebo on cardiovascular risk factors in postmenopausal women.

studies employing progestins with a more-androgenic profile (11, 21, 48) from subgroup analyses of low-dose HT vs conventional dose, the heterogeneity was reduced to 0% with no change in the effects on HDL-C (0.25 mg/dL; 95% CI, −1.89–2.39; $I^2$, 0%, data not shown).

### Triglycerides

No significant effects were observed for the comparison of low-dose HT with placebo (−3.59 mg/dL; 95% CI, −15.74–8.55) or conventional-dose HT (−10.69 mg/dL; 95% CI, −21.99–0.61) (Figures 3 and 4). Significant heterogeneity was observed in both subgroups. Sensitivity analyses of oral agents showed significantly lower levels of triglycerides in the low-dose group vs conventional-dose group (−14.09 mg/dL; 95% CI, −24.2–−3.93; $P < .01$) (data not shown). For oral low-dose HT compared with placebo, no significant differences were observed (1.01 mg/dL; 95% CI, −13.5–11.5) (data not shown).

Removal of two unopposed estrogen studies (49, 50) resulted in a decrease in heterogeneity and in significantly lower levels of triglycerides when oral low-dose HT was compared with oral conventional dose (−11.1 mg/dL; 95% CI, 17.1–−5.02, $I^2$, 0%) (data not shown).

## Discussion

In this systematic review with meta-analysis of low-dose HT RCTs, 28 clinical trials were pooled for a total of 3360 postmenopausal women without overt clinical disease. Mean age was 54.7 years, and mean followup was 11.3 months. In this population of apparently healthy postmenopausal women, the effect of low-dose HT did not differ from that of placebo or conventional-dose HT regarding weight, BMI, BP, CRP, or HDL-C. In contrast, whereas low-dose HT induced lower TC and LDL-C levels compared with placebo, these effects were less effective

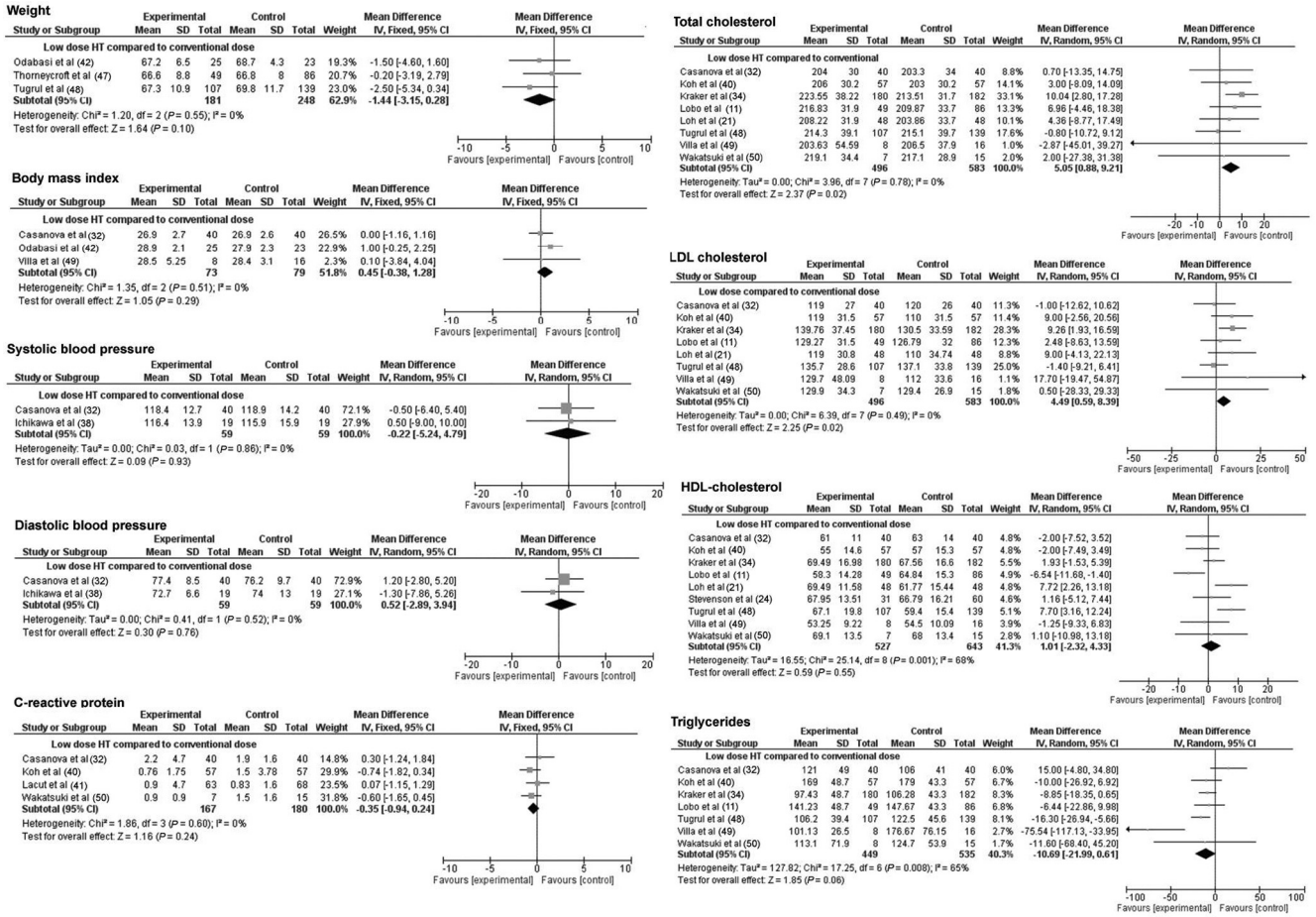


**Figure 4.** Effects of low-dose HT compared with conventional-dose HT on cardiovascular risk factors in postmenopausal women.

than those observed with conventional-dose HT. Triglyceride levels were lower with oral low-dose HT compared with conventional-dose HT, and similar to the levels found with placebo.

We found only four studies assessing the effects of low-dose HT on body weight, and the results suggest no changes in weight after treatment. Springer et al (59), looking for the effects of HT on body weight and its association with leptin levels, also found that the available literature does not provide evidence for an effect of HT in attenuating weight gain in postmenopausal women. Gravena et al (60), in a population-based study of 456 Brazilian postmenopausal women, found that one of the factors most strongly associated with overweight at this stage of life was not using HT. A review that aimed to summarize the literature regarding the effect of the menopause on body weight and body composition concluded that estrogen-only or estrogen-progestin therapy does not adversely affect body weight and may ameliorate accumulation of abdominal fat (61–63). Reduction of central fat accumulation was also observed in clinical trials with low-dose HT (56). The North American Menopause Society states that hormonal therapy, regardless of type (estrogen or estrogen-progestin), does not cause overweight (20). Data regarding the effects of HT on BP in postmenopausal women with and without hypertension are controversial. In our meta-analyses, we found nine trials with low-dose HT in nonhypertensive women, and low-dose HT was not associated with changes in BP. Four studies (32, 35, 46, 58) reporting the effects of 1 mg estradiol associated with drospirenone, in nonhypertensive women, showed neutral effect on BP. Angerer et al (29) and Bingol et al (30), studying 1 mg oral estradiol associated with gestodene and norethisterone acetate (NETA), respectively, found a reduction in diastolic BP, whereas systolic BP remained unchanged. In contrast, the WHI study (3) found a significant increase in systolic BP in women on HT vs placebo after 2 years of therapy. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (64) also found an increase in systolic BP in all HT groups after 3 years. Differences among trials may be attributable to several factors. Both WHI and PEPI trials used conventional doses of HT and conjugated equine estrogens. In addition, progestin regimens also differed.

In the present study, CRP remained unchanged after low-dose HT. We also found a trend toward higher CRP

when comparing full-dose HT with low-dose oral HT, although this result should be regarded with caution because of the small number of studies. An increase in CRP levels has been consistently observed (8, 64, 65) after administration of oral agents in conventional doses (66). A study comparing the effects of oral and nonoral HT on CRP reported significant differences (66). In fact, current literature data suggest a neutral profile of nonoral HT on CRP (67, 68). Although CRP levels may be regarded as a predictor of coronary heart disease, mortality, and stroke (69), the relationship between increased CRP in postmenopausal women after HT and CV events is complex and unclear.

We observed a significant reduction in TC and LDL-C in the low-dose group compared with placebo. When low-dose HT was compared with full-dose HT, the full dose was more effective in reducing TC and LDL-C. These results confirm previously published data on the effects of HT on lipids (55, 66). In the present review, we observed a reduction in triglycerides when using low-dose oral HT. A dose-dependent effect of oral HT on triglycerides has been reported (11, 70), as well as different effects of oral and nonoral HT on triglycerides (66, 71). Transdermal-administered estrogen has less effect on serum lipids, probably due to the bypass of portal circulation, and thus a minimal effect on hepatic metabolism (72). We were not able to assess differences between oral and nonoral low-dose HT with respect to effects on lipids because only one study focusing on lipids and analyzing low-dose nonoral HT was available (31).

Godsland (71) reviewed 248 studies published between 1974 and 2000 and reported an association of estrogen HT with decreased in TC and LDL-C. Salpeter et al (66), in a meta-analysis evaluating the effect of HT on components of the metabolic syndrome, also described a reduction in TC following HT. In addition, those authors observed reduced abdominal fat, mean arterial BP, and increased levels of CRP after HT. Yet another systematic review (73) reported a neutral effect of TH on BMI. A difference between the present study and previous reviews is dose stratification, which was had not been previously performed.

There was significant heterogeneity in the analyses of HDL-C, limiting the interpretation of the present data and suggesting an absence of effects of low-dose HT on HDL-C. Other studies have discussed whether different types and regimens (cyclic or continuous) of progestins can influence HDL-C levels (51, 53, 67, 72). More androgenic progestins may have an action on the reduction of HDL-C (52). The application of sensitivity analyses to explain heterogeneity showed that removing studies with more androgenic progestins (11, 21, 48) resulted in heterogeneity ($I^2$) of 0% and unchanged HDL-C levels. These findings lead to other intriguing questions regarding the relationship between estrogen doses and cyclic or continuous progestin regimens (15, 72, 74).

Limitations of the present study include 1) the reduced number of studies for some variables, 2) different HT doses and regimens and different types of estrogen and progestins, 3) different lengths of followup among the pooled studies, 4) different time since menopause when HT was administered, and 5) limiting the language of publication to English. These limitations highlight the need for further clinical trials to clarify the observed interactions between doses of HT and systemic effects.

In conclusion, the present results support the notion that low-dose HT does not differ from placebo or conventional-dose HT regarding effects on weight, BMI, BP, CRP, or HDL-C in younger and apparently healthy postmenopausal women. Low-dose HT was associated with better lipid profile compared with placebo, and induced higher total and LDL-C and lower triglycerides vs conventional-dose HT. Additional studies are needed to explain the mechanisms involved in the effects of low-dose HT as well as different routes of administration on traditional and nonconventional CV risk factors.

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## References

1. **Hickey M, Davis SR, Sturdee DW.** Treatment of menopausal symptoms: What shall we do now? *Lancet*. 2005;366:409–421.
2. **Yang D, Li J, Yuan Z, Liu X.** Effect of hormone replacement therapy on cardiovascular outcomes: A meta-analysis of randomized controlled trials. *PLoS One*. 2013;8:e62329.
3. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
4. **Wassertheil-Smoller S, Hendrix SL, Limacher M, et al.** Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: A randomized trial. *JAMA*. 2003;289:2673–2684.
5. **Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE,**

**Stampfer MJ.** A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;133:933–941.
6. **Bush TL, Barrett-Connor E, Cowan LD, et al.** Cardiovascular mortality and noncontraceptive use of estrogen in women: Results from the Lipid Research Clinics Program Follow-up Study. *Circulation*. 1987;75:1102–1109.
7. **Rossouw JE, Prentice RL, Manson JE, et al.** Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465–1477.
8. **Rossouw JE, Cushman M, Greenland P, et al.** Inflammatory, lipid, thrombotic, and genetic markers of coronary heart disease risk in the women's health initiative trials of hormone therapy. *Arch Intern Med*. 2008;168:2245–2253.
9. **Bray PF, Larson JC, Lacroix AZ, et al.** Usefulness of baseline lipids and C-reactive protein in women receiving menopausal hormone therapy as predictors of treatment-related coronary events. *Am J Cardiol*. 2008;101:1599–1605.
10. **Harman SM, Naftolin F, Brinton EA, Judelson DR.** Is the estrogen controversy over? Deconstructing the Women's Health Initiative study: A critical evaluation of the evidence. *Ann N Y Acad Sci*. 2005;1052:43–56.
11. **Lobo RA, Bush T, Carr BR, Pickar JH.** Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. *Fertil Steril*. 2001;76:13–24.
12. **Manson JE, Bassuk SS, Harman SM, et al.** Postmenopausal hormone therapy: New questions and the case for new clinical trials. *Menopause*. 2006;13:139–147.
13. **Harman SM, Brinton EA, Cedars M, et al.** KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric*. 2005;8:3–12.
14. **Smiley DA, Khalil RA.** Estrogenic compounds, estrogen receptors and vascular cell signaling in the aging blood vessels. *Curr Med Chem*. 2009;16:1863–1887.
15. **Panay N.** Estrogen dose: The cardiovascular impact. *Climacteric*. 2009;12:91–95.
16. **Olié V, Canonico M, Scarabin PY.** Postmenopausal hormone therapy and venous thromboembolism. *Thromb Res*. 2011;127: S26–29.
17. **Renoux C, Dell'Aniello S, Suissa S.** Hormone replacement therapy and the risk of venous thromboembolism: A population-based study. *J Thromb Haemost*. 2010;8:979–986.
18. **Harvey PJ, Molloy D, Upton J, Wing LM.** Dose response effect of conjugated equine oestrogen on blood pressure in postmenopausal women with hypertension. *Blood Press*. 2000;9:275–282.
19. **Renoux C, Dell'aniello S, Garbe E, Suissa S.** Transdermal and oral hormone replacement therapy and the risk of stroke: A nested case-control study. *BMJ*. 2010;340:c2519.
20. **North American Menopause Society.** The 2012 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2012;19:257–271.
21. **Loh FH, Chen LH, Yu SL, Jorgensen LN.** The efficacy of two dosages of a continuous combined hormone replacement regimen. *Maturitas*. 2002;41:123–131.
22. **van Baal WM, Kenemans P, Emeis JJ, et al.** Long-term effects of combined hormone replacement therapy on markers of endothelial function and inflammatory activity in healthy postmenopausal women. *Fertil Steril*. 1999;71:663–670.
23. **Godsland IF, Manassiev NA, Felton CV, et al.** Effects of low and high dose oestradiol and dydrogesterone therapy on insulin and lipoprotein metabolism in healthy postmenopausal women. *Clin Endocrinol (Oxf)*. 2004;60:541–549.
24. **Stevenson JC, Rioux JE, Komer L, Gelfand M.** 1 and 2 mg 17beta-estradiol combined with sequential dydrogesterone have similar effects on the serum lipid profile of postmenopausal women. *Climacteric*. 2005;8:352–359.
25. **Shufelt CL, Merz CN, Prentice RL, et al.** Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: Findings from the Women's Health Initiative Observational Study. *Menopause*. 2014;21:260–266.
26. **Moher D, Altman DG, Liberati A, Tetzlaff J.** PRISMA statement. *Epidemiology*. 2011;22:128; author reply 128.
27. **Devissaguet JP, Brion N, Lhote O, Deloffre P.** Pulsed estrogen therapy: Pharmacokinetics of intranasal 17-beta-estradiol (S21400) in postmenopausal women and comparison with oral and transdermal formulations. *Eur J Drug Metab Pharmacokinet*. 1999;24:265–271.
28. **Alexandersen P, Riis BJ, Stakkestad JA, Delmas PD, Christiansen C.** Efficacy of levormeloxifene in the prevention of postmenopausal bone loss and on the lipid profile compared to low dose hormone replacement therapy. *J Clin Endocrinol Metab*. 2001;86:755–760.
29. **Angerer P, Störk S, von Schacky C.** Influence of 17beta-oestradiol on blood pressure of postmenopausal women at high vascular risk. *J Hypertens*. 2001;19:2135–2142.
30. **Bingol B, Gunenc Z, Yilmaz M, Biri A, Tiras B, Güner H.** Effects of hormone replacement therapy on glucose and lipid profiles and on cardiovascular risk parameters in postmenopausal women. *Arch Gynecol Obstet*. 2010;281:857–864.
31. **Brynhildsen J, Hammar M.** Lipids and clotting factors during low dose transdermal estradiol/norethisterone use. *Maturitas*. 2005;50: 344–352.
32. **Casanova G, Radavelli S, Lhullier F, Spritzer PM.** Effects of nonoral estradiol-micronized progesterone or low-dose oral estradiol-drospirenone therapy on metabolic variables and markers of endothelial function in early postmenopause. *Fertil and Steril*. 2009;92:605–612.
33. **Davidson MH, Maki KC, Marx P, et al.** Effects of continuous estrogen and estrogen-progestin replacement regimens on cardiovascular risk markers in postmenopausal women. *Arch Intern Med*. 2000;160:3315–3325.
34. **de Kraker AT, Kenemans P, Smolders RG, Kroeks MV, van der Mooren MJ.** The effects of 17 beta-oestradiol plus dydrogesterone compared with conjugated equine oestrogens plus medroxyprogesterone acetate on lipids, apolipoproteins and lipoprotein(a). *Maturitas*. 2004;49:253–263.
35. **Gambacciani M, Rosano G, Cappagli B, Pepe A, Vitale C, Genazzani AR.** Clinical and metabolic effects of drospirenone-estradiol in menopausal women: A prospective study. *Climacteric*. 2011;14:18–24.
36. **Hemelaar M, van der Mooren MJ, Mijatovic V, et al.** Oral, more than transdermal, estrogen therapy improves lipids and lipoprotein(a) in postmenopausal women: A randomized, placebo-controlled study. *Menopause*. 2003;10:550–558.
37. **Hwang J, Mack WJ, Xiang M, Sevanian A, Lobo RA, Hodis HN.** Long-term effect of estrogen replacement on plasma nitric oxide levels: Results from the estrogen in the prevention of atherosclerosis trial (EPAT). *Atherosclerosis*. 2005;181:375–380.
38. **Ichikawa J, Sumino H, Ichikawa S, Ozaki M.** different effects of transdermal and oral hormone replacement therapy on the renin-angiotensin system, plasma bradykinin level, and blood pressure of normotensive postmenopausal women. *Am J Hypertens*. 2006;19: 744–749.
39. **Kaya C, Cengiz SD, Cengiz B, Akgun G.** Long-term effects of low-dose 17beta-estradiol plus dydrogesterone on 24-h ambulatory blood pressure in healthy postmenopausal women: A 1-year, randomized, prospective study. *Gynecol Endocrinol*. 2007;23:62–67.
40. **Koh KK, Shin MS, Sakuma I, et al.** Effects of conventional or lower doses of hormone replacement therapy in postmenopausal women. *Arterioscler Thromb Vasc Biol*. 2004;24:1516–1521.
41. **Lacut K, Oger E, Le Gal G, et al.** Differential effects of oral and transdermal postmenopausal estrogen replacement therapies on C-reactive protein. *Thromb Haemost*. 2003;90:124–131.
42. **Odabasi AR, Yuksel H, Karul A, Kozaci D, Sezer SD, Onur E.** Effects of standard and low dose 17beta-estradiol plus norethisterone acetate on body composition and leptin in postmenopausal women at

risk of body mass index and waist girth related cardiovascular and metabolic disease. *Saudi Med J*. 2007;28:855–861.
43. **Samsioe G, Li C, Borgfeldt C, Wilawan K, Aberg A, Larsen S.** Changes in lipid and lipoprotein profile in postmenopausal women receiving low-dose combinations of 17beta-estradiol and norethisterone acetate. *Menopause*. 2002;9:335–342.
44. **Steiner AZ, Hodis HN, Lobo RA, Shoupe D, Xiang M, Mack WJ.** Postmenopausal oral estrogen therapy and blood pressure in normotensive and hypertensive subjects: The Estrogen in the Prevention of Atherosclerosis Trial. *Menopause*. 2005;12:728–733.
45. **Störk S, Von Schacky C, Angerer P.** The effect of 17beta-estradiol on endothelial and inflammatory markers in postmenopausal women: A randomized, controlled trial. *Atherosclerosis*. 2002;165:301–307.
46. **Tankó LB, Christiansen C.** Effects of 17beta-oestradiol plus different doses of drospirenone on adipose tissue, adiponectin and atherogenic metabolites in postmenopausal women. *J Intern Med*. 2005; 258:544–553.
47. **Thorneycroft IH, Lindsay R, Pickar JH.** Body composition during treatment with conjugated estrogens with and without medroxyprogesterone acetate: Analysis of the women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial. *Am J Obstet Gynecol* 2007; 197:137 e131–e137.
48. **Tugrul S, Yildirim G, Pekin O, Uslu H, Kutlu T, Eren S.** Comparison of two forms of continuous combined hormone replacement therapy with respect to metabolic effects. *Arch Gynecol Obstet*. 2007;275: 335–339.
49. **Villa P, Sagnella F, Perri C, et al.** Low- and standard-estrogen dosage in oral therapy: Dose-dependent effects on insulin and lipid metabolism in healthy postmenopausal women. *Climacteric*. 2008;11: 498–508.
50. **Wakatsuki A, Ikenoue N, Shinohara K, Watanabe K, Fukaya T.** Effect of lower dosage of oral conjugated equine estrogen on inflammatory markers and endothelial function in healthy postmenopausal women. *Arterioscler Thromb Vasc Biol*. 2004;24:571–576.
51. **Archer DF, Thorneycroft IH, Foegh M, et al.** Long-term safety of drospirenone-estradiol for hormone therapy: A randomized, double-blind, multicenter trial. *Menopause*. 2005;12:716–727.
52. **Endrikat J, Lange E, Kunz M, Schmidt W, Graeser T.** A one-year randomized double-blind, multicentre study to evaluate the effects of an oestrogen-reduced, continuous combined hormone replacement therapy preparation containing 1 mg oestradiol valerate and 2 mg dienogest on metabolism in postmenopausal women. *Eur J Contracept Reprod Health Care*. 2007;12:229–239.
53. **Langer RD, Friedman AJ.** Effects of E2 and E2/norgestimate hormone therapy on elevated baseline lipids. *J Reprod Med*. 2006;51: 610–616.
54. **Lobo RA, Zacur HZ, Caubel P, Lane R.** A novel intermittent regimen of norgestimate to preserve the beneficial effects of 17beta-estradiol on lipid and lipoprotein profiles. *Am J Obstet Gynecol*. 2000;182:41–49.
55. **Pornel B, Chevallier O, Netelenbos JC.** Oral 17beta-estradiol (1 mg) continuously combined with dydrogesterone improves the serum lipid profile of postmenopausal women. *Menopause*. 2002;9:171–178.
56. **Yüksel H, Odabasi AR, Demircan S, Köseoglu K, Kizilkaya K, Onur E.** Effects of postmenopausal hormone replacement therapy on body fat composition. *Gynecol Endocrinol*. 2007;23:99–104.
57. **Ylikorkala O, Lim P, Caubel P.** Effects on serum lipid profiles of continuous 17beta-estradiol, intermittent norgestimate regimens versus continuous combined 17beta-estradiol/norethisterone acetate hormone replacement therapy. *Clinical Ther*. 2000;22:622–636.
58. **Villa P, Suriano R, Ricciardi L, et al.** Low-dose estrogen and drospirenone combination: Effects on glycoinsulinemic metabolism and other cardiovascular risk factors in healthy postmenopausal women. *Fertil Steril*. 2011;95:158–163.
59. **Springer AM, Foster-Schubert K, Morton GJ, Schur EA.** Is there evidence that estrogen therapy promotes weight maintenance via effects on leptin? *Menopause*. 2014;21:424–432.
60. **Gravena AA, Brischiliari SC, Lopes TC, Agnolo CM, Carvalho MD, Pelloso SM.** Excess weight and abdominal obesity in postmenopausal Brazilian women: A population-based study. *BMC Womens Health*. 2013;13:46.
61. **Davis SR, Castelo-Branco C, Chedraui P, et al.** Understanding weight gain at menopause. *Climacteric*. 2012;15:419–429.
62. **Spritzer PM, Oppermann K.** Weight gain and abdominal obesity at menopause. *Climacteric*. 2013;16:292.
63. **Sutton-Tyrrell K, Zhao X, Santoro N, et al.** Reproductive hormones and obesity: 9 years of observation from the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2010;171:1203–1213.
64. **Cushman M, Legault C, Barrett-Connor E, et al.** Effect of postmenopausal hormones on inflammation-sensitive proteins: The Postmenopausal Estrogen/Progestin Interventions (PEPI) study. *Circulation*. 1999;100:717–722.
65. **Grady D, Herrington D, Bittner V, et al.** Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002; 288:49–57.
66. **Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE.** Meta-analysis: Effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes Obes Metab*. 2006;8:538–554.
67. **Casanova G, Spritzer PM.** Effects of micronized progesterone added to non-oral estradiol on lipids and cardiovascular risk factors in early postmenopause: A clinical trial. *Lipids Health Dis*. 2012;11: 133.
68. **Vongpatanasin W, Tuncel M, Wang Z, Arbique D, Mehrad B, Jialal I.** Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. *J Am Coll Cardiol*. 2003;41:1358–1363.
69. **Kaptoge S, Di Angelantonio E, Lowe G, et al.** C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: An individual participant meta-analysis. *Lancet*. 2010;375: 132–140.
70. **Schlegel W, Petersdorf LI, Junker R, Schulte H, Ebert C, Von Eckardstein A.** The effects of six months of treatment with a low-dose of conjugated oestrogens in menopausal women. *Clin Endocrinol (Oxf)*. 1999;51:643–651.
71. **Godsland IF.** Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: Analysis of studies published from 1974–2000. *Fertil Steril*. 2001; 75:898–915.
72. **Mikkola TS, Clarkson TB.** Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res*. 2002;53:605–619.
73. **Norman RJ, Flight IH, Rees MC.** Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: Weight and body fat distribution. *Cochrane Database Syst Rev*. 2000;2:CD001018.
74. **Khalil RA.** Estrogen, vascular estrogen receptor and hormone therapy in postmenopausal vascular disease. *Biochem Pharmacol*. 2013; 86:1627–1642.