

Low & Ultra Low Dose HRT The Cardiovascular Impact

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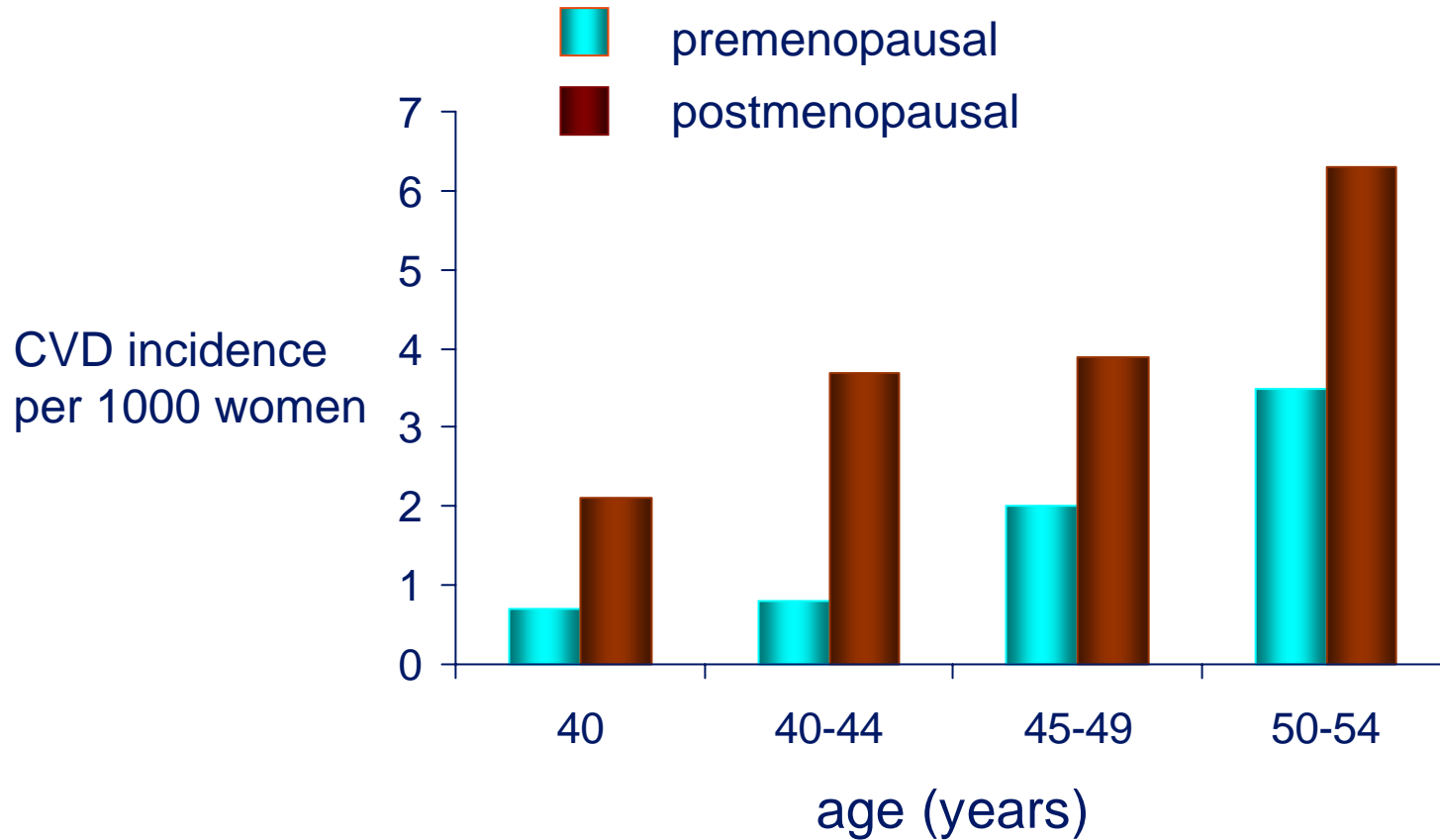
West London Menopause & PMS Centre

Low & Ultra Low Dose HRT

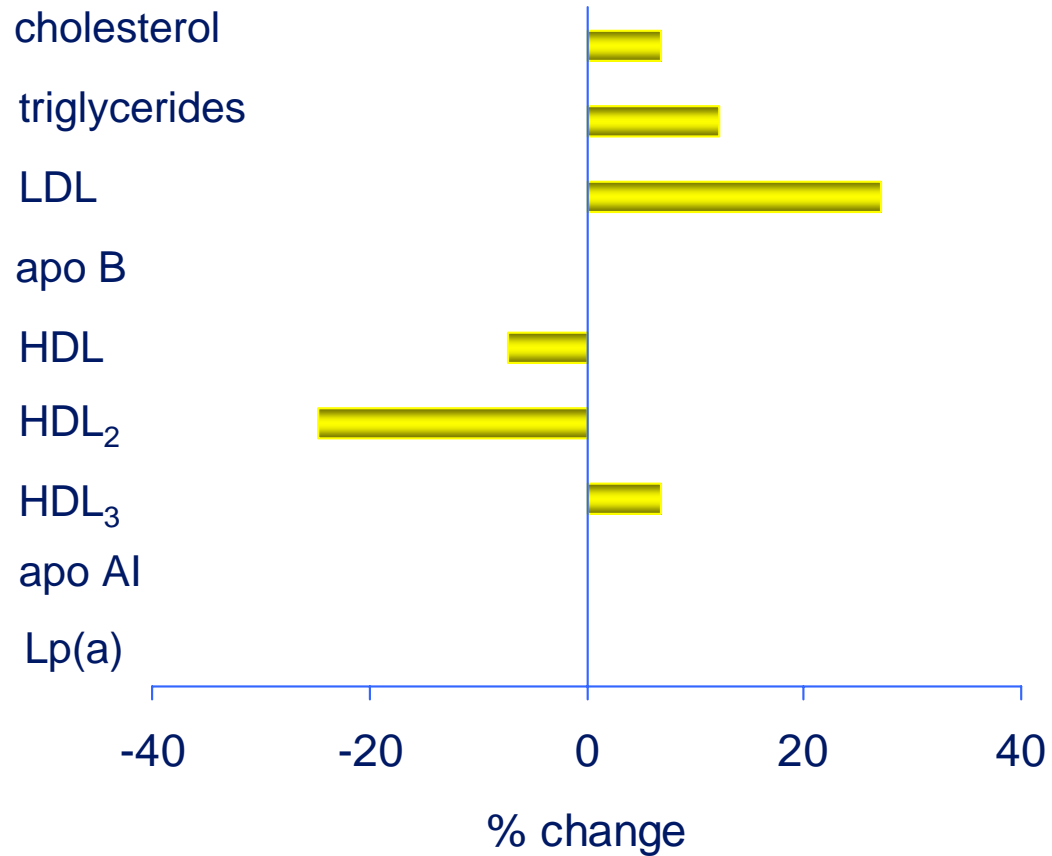
The Cardiovascular Impact

- Impact of menopause on cardiovascular disease
- HT & Cardiovascular Disease – where are we now?
- What is and Why Use Low dose HT?
- Effect of Low dose HT Regimens on Cardiovascular Disease
 - Low dose HT as primary prevention
 - Low dose HT as secondary prevention
- Future Studies

CVD AND MENOPAUSAL STATUS

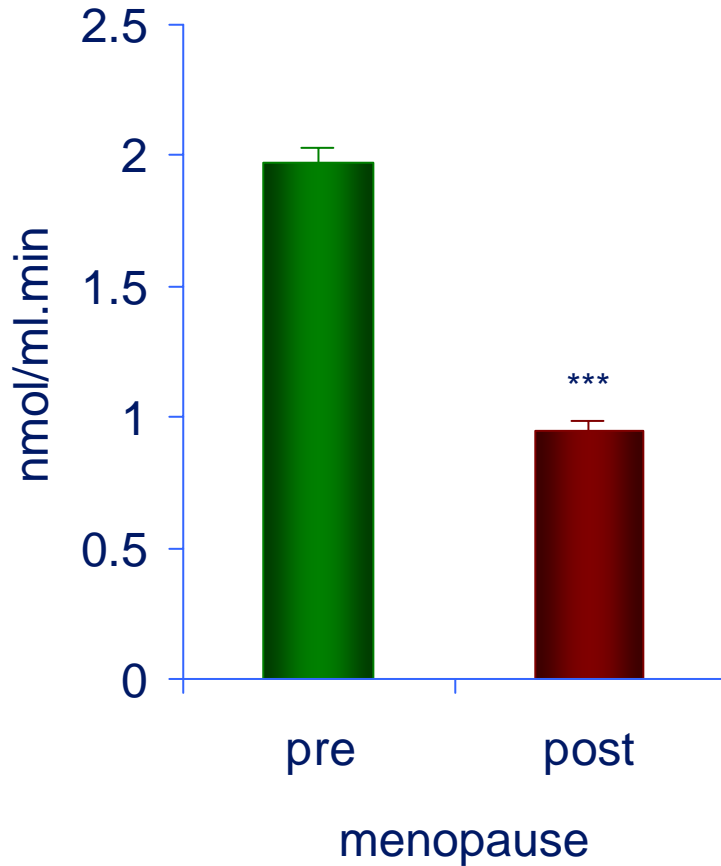


MENOPAUSE AND LIPIDS

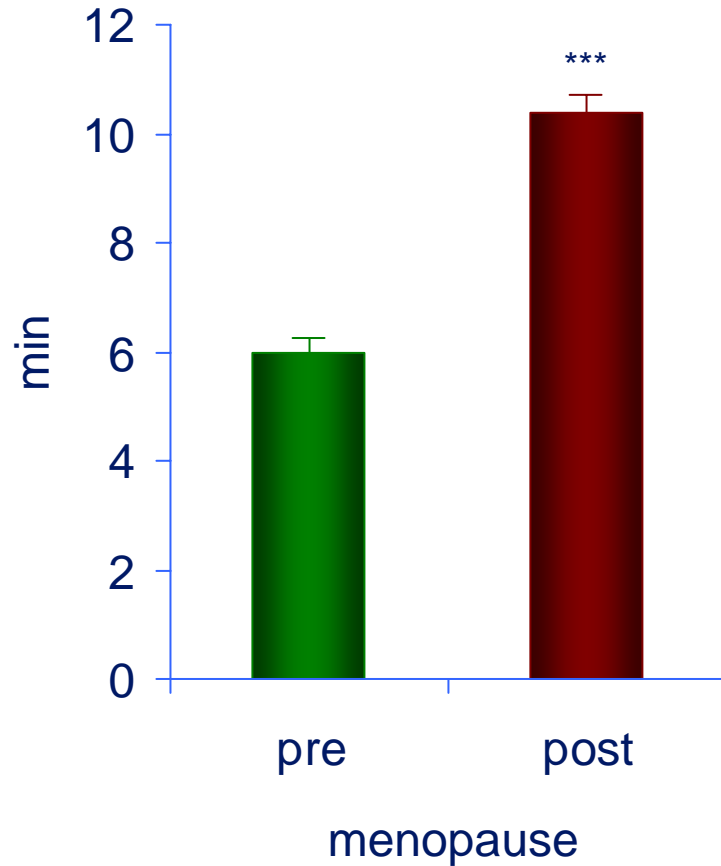


INSULIN METABOLISM

incremental pancreatic
insulin secretion



insulin half-life



***p<0.001

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Low & Ultra Low Dose HRT

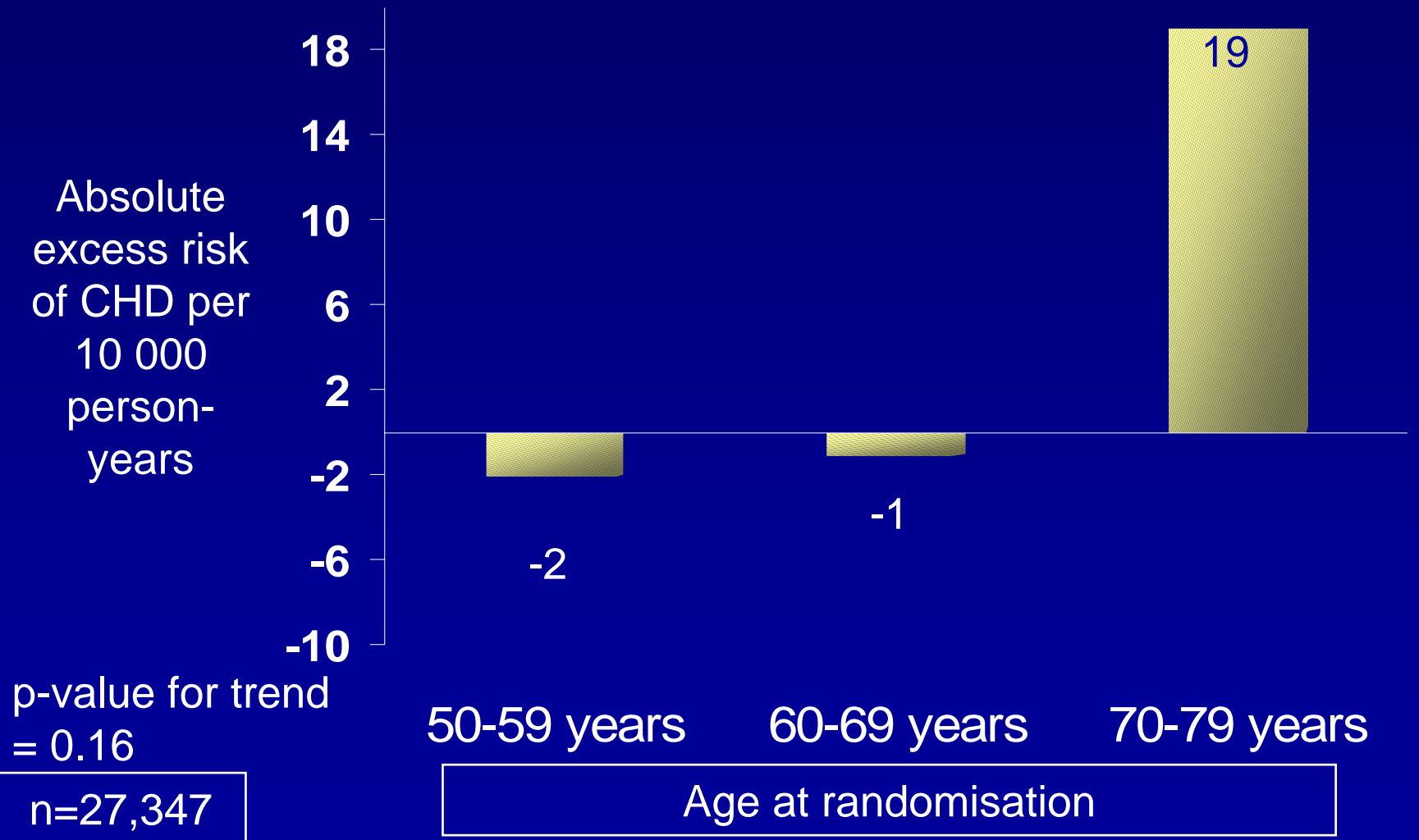
The Cardiovascular Impact

- **CVD**

- There is evidence that HT may be cardioprotective if started around the time of menopause and continued long-term (often referred to as the 'window of opportunity' concept).
- In women less than 60 years old, recently menopausal, without prevalent cardiovascular disease, the initiation of MHT does not cause early harm, and may reduce cardiovascular morbidity and mortality.
- HT improves many aspects of the metabolic syndrome and reduces the risk of diabetes

Coronary Heart Disease

HRT and CHD: Absolute risk by age



Why is the CVD risk increased with HT in older age groups?

- **HERS and WHI – initial harm followed by later benefit**
- **“Inappropriately high doses of oestrogen could cause cardiovascular harm due to transient disturbances in thrombogenesis and vascular remodelling.**
- **Oestrogen affects both coagulation and fibrinolysis**
- **At relatively high doses (for age group) there may be an overall increase in thrombogenesis, plaque progression or instability**
- **Can we avoid initial harm in older age groups / secondary prevention by using low dose HT?**

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Low dose HRT

What is it?

| | Ultra Low | Low | Standard | High |
|---|-------------------|-----|----------|------|
| Conjugated equine estrogens (mg) | 0.15 ¹ | 0.3 | 0.625 | 1.25 |
| Micronised 17 β -estradiol (mg) | 0.5 ² | 1 | 2 | 4 |
| Estradiol valerate (mg) | | 1 | 2 | |
| Transdermal 17 β -estradiol (mcg) | 14 ³ | 25 | 50 | 100 |

Gambacciani M, Genazzani AR. *Maturitas* 40 (2001)

¹ Lindsay et al *Obstet Gynecol* (1984)

² Panay et al *CHOICE Climacteric* (2007)

³ Ettinger et al *Obstet Gynecol* (2004)

Modern prescribing principles

- Why low dose HRT?
- Menopausal symptoms may be controlled by lower HRT doses than previously used
 - (Notelovitz et al *Obstet Gynecol* 2000)
 - (Panay et al *CHOICE Climacteric* 2007)
- Lower doses have also been shown to prevent osteoporosis
 - (Lindsay *JAMA* 2002 (HOPE 0.3mg CEE/1.5MPA))
 - (Ettinger *Supp J Fam Plann* 2004 (14mcg TD E2))
 - (Greenwald et al *Menopause* 2005 (0.25mg oral E2))

Modern prescribing principles

- Why low dose HRT?
- Fewer minor adverse events – oestrogenic and progestogenic
- There are fewer major adverse effects at lower doses, i.e. VTE & Stroke & ?CHD
 - (Jick et al *Lancet* 1996)
 - (Grodstein et al *Ann Intern Med* 2000)

VTE & OESTROGEN DOSE

- Possible risk decrease with lowering the dose of oestrogen

- CEE 1.25 mg RR 6.9
- CEE 0.625 mg RR 3.3
- CEE 0.3 mg RR 2.1

STROKE & HRT: DOSE EFFECT

- CEE 1.25 mg RR 1.58 (1.16-2.15)
 - CEE 0.625 mg RR 1.11 (0.90-1.37)
 - CEE 0.3 mg RR 0.43 (0.22-0.83)
-
- But what about reducing the dose in CHD?

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The effects of six months of treatment with a low-dose of conjugated oestrogens in menopausal women

- Open trial study, 3 groups small numbers (12 per group) of early postmenopausal German women on 0.3mg / 0.6mg / 1.25mg
- D1-D10 CEE alone D11- D21 5mg medrogestone
- Fasting samples D10 / 21 / 28 & 1st 3rd 6th month on treatment

The effects of six months of treatment with a low-dose of conjugated oestrogens in menopausal women

- Results
- 0.3mg CEE lowered Total Chol / LDL Chol without adverse effects on TGs and factor VIIc (observed at higher doses)
- However, LDL / HDL effects were greater with higher doses – is this important??

HOPE TRIAL

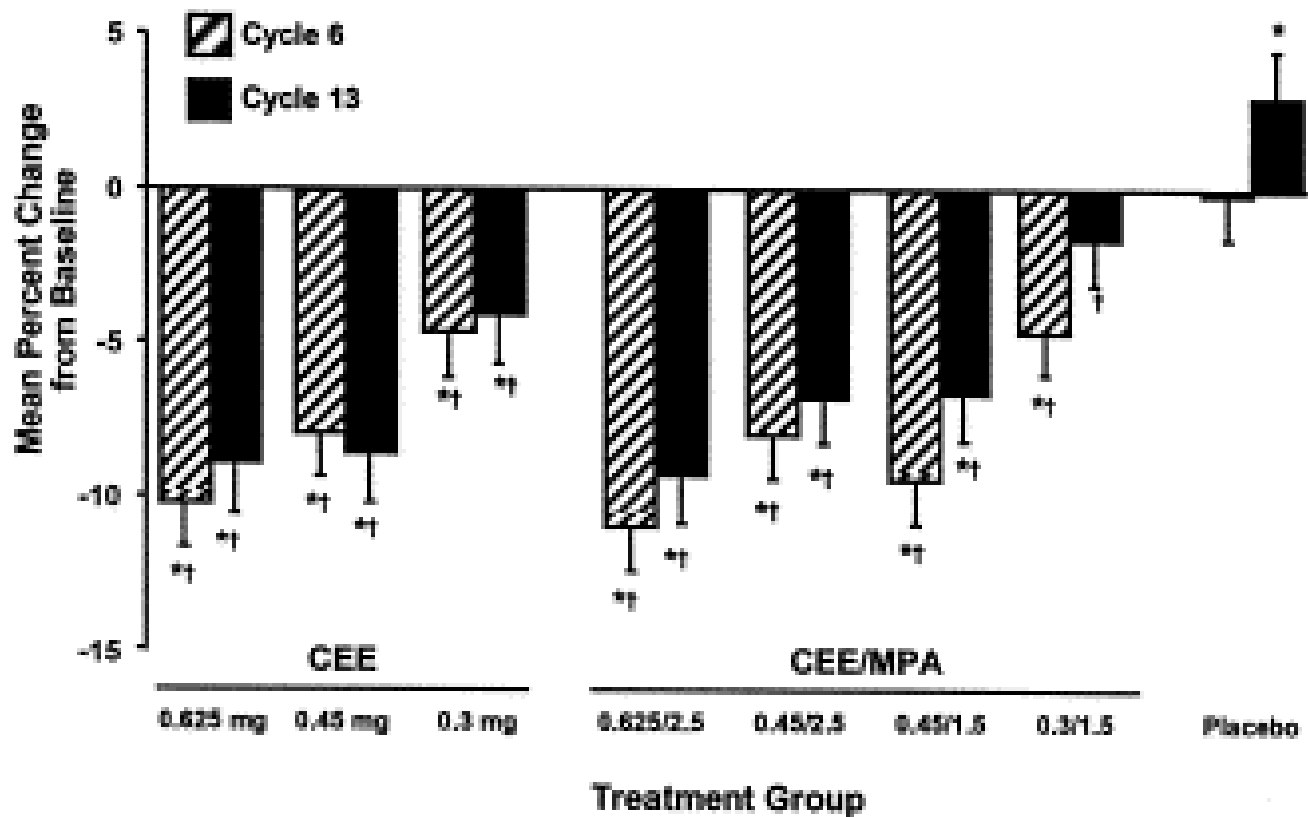
- 749 of the 2673 postmenopausal women in the original trial (28%) entered metabolic trial
- 40 – 65 years < 4 years from last menses
- Within 20% of normal BMI (<35)
- Lipids, lipoproteins, glucose tolerance, coagulation, fibrinolytic factors
- Baseline, Cycle 6 and 1 year

HOPE TRIAL - groups

- CEE 0.625mg n = 97
- CEE 0.625mg / MPA 2.5mg n = 86
- CEE 0.45mg n = 95
- CEE 0.45mg / MPA 2.5mg n = 96
- CEE 0.45mg / MPA 1.5mg n = 94
- CEE 0.3mg n = 89
- CEE 0.3mg / MPA 1.5mg n = 98
- Placebo n = 94

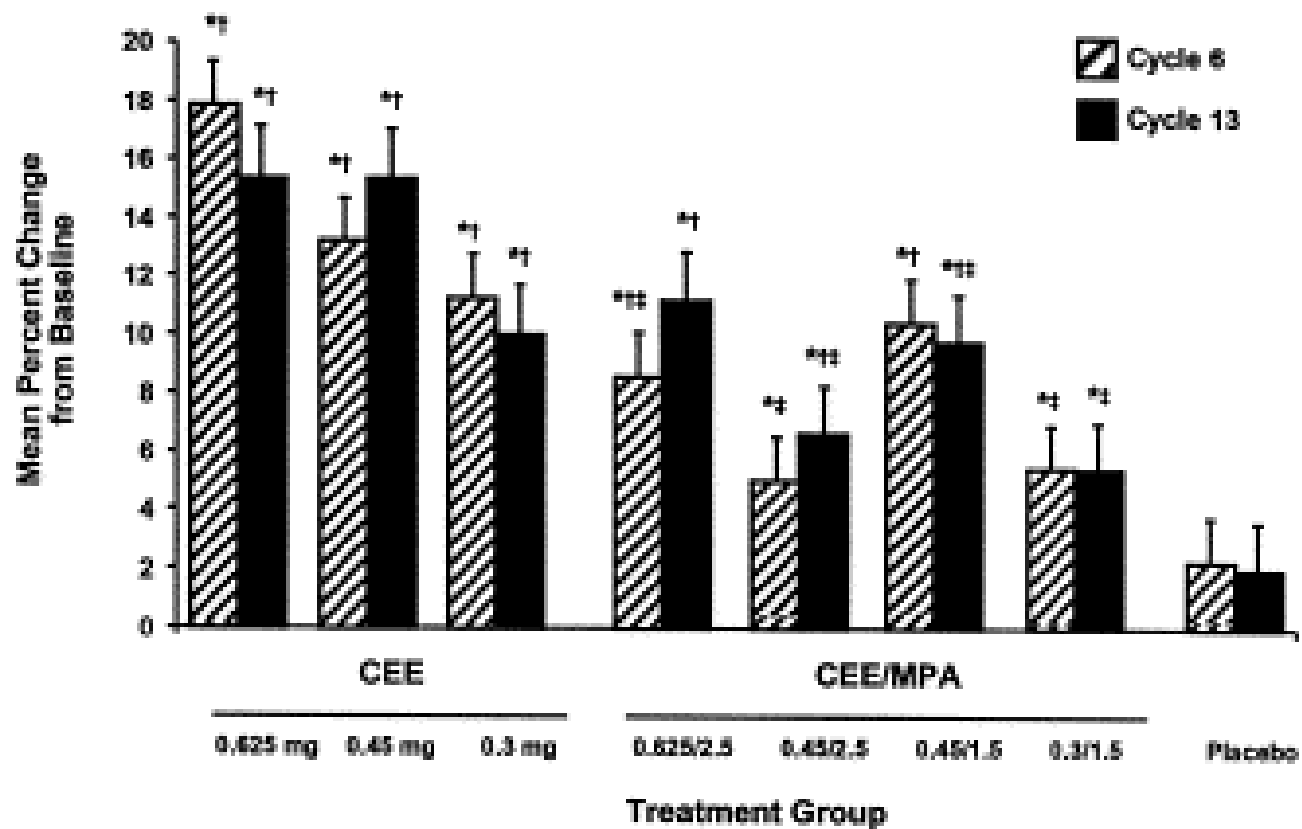
HOPE TRIAL

LDL-Cholesterol



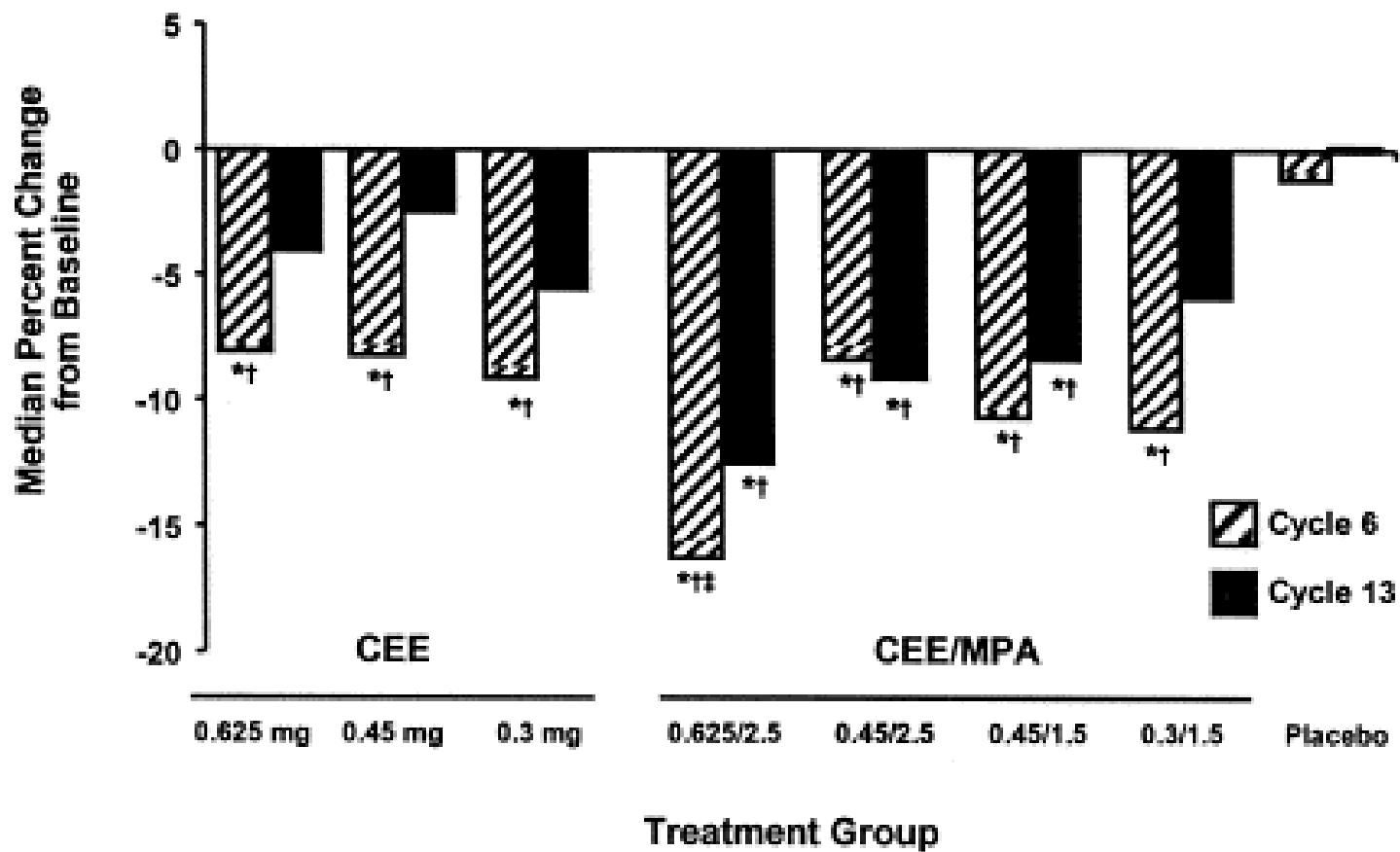
HOPE TRIAL

HDL-Cholesterol



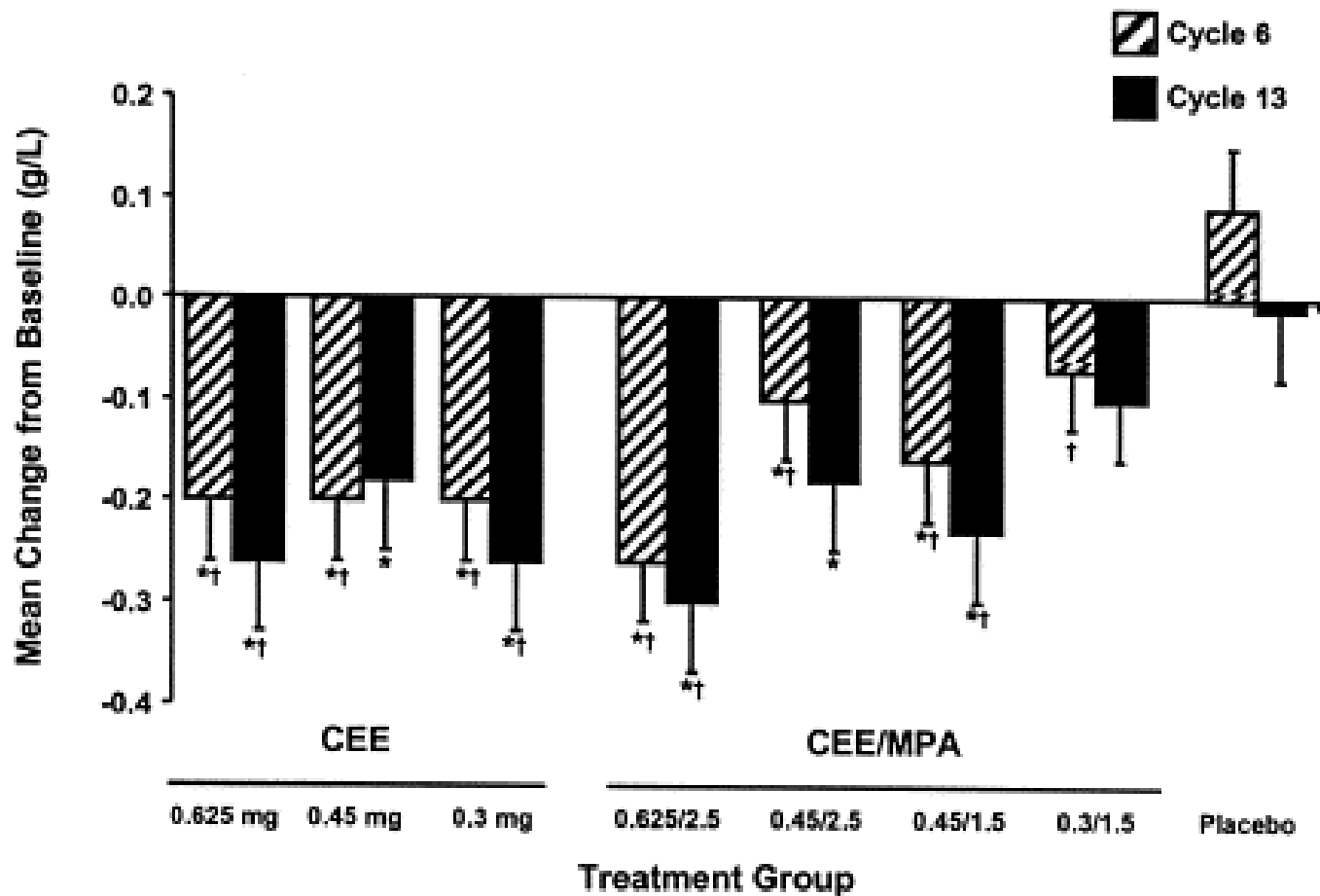
HOPE TRIAL

Lp(a)



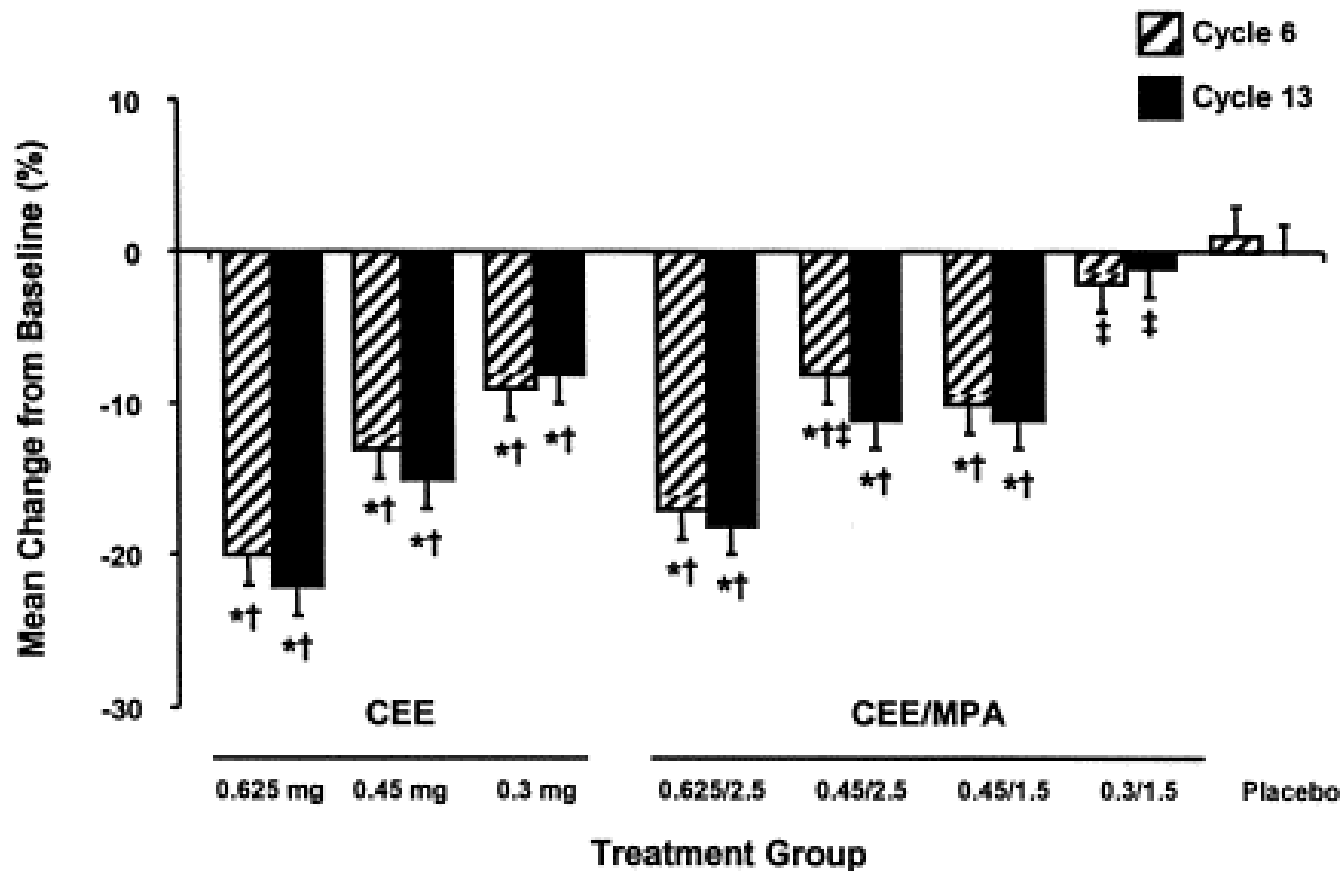
HOPE TRIAL

Fibrinogen Activity



HOPE TRIAL

Protein S Activity



HOPE TRIAL (metabolic data)

- **Fasting Glucose**
- Minimal changes observed in carbohydrate metabolism over time for all groups
- Decrease in baseline for fasting glucose only significant for CEE 0.625mg / MPA 2.5mg at both time points

HOPE TRIAL summary

- Lower dose CEE / MPA combinations produced less marked effects on LDL & HDL but with minimal impact on TG's and haemostatic factors
- Thus, lower doses may be appropriate for older age group women as well as early postmenopausal women in avoiding initial CV harm whilst maintaining benefits

Arterial stiffness (compliance) and hormone replacement therapy

- Arterial function measurements increasingly used as surrogate markers of CVD
- Increased arterial stiffness shown to be an independent marker of CVD risk
- Arterial stiffness increases with age
- Central arterial stiffness is associated with atherosclerosis
- Observational studies showing HRT users have more compliant arteries than non users

A Comparison of Low-Dose and Standard-Dose Oral Estrogen on Forearm Endothelial Function in Early Postmenopausal Women

- 55 Postmenopausal Japanese women mean age 54 (47 – 57)
- Conjugated equine estrogen (CEE, 0.625 mg) plus medroxyprogesterone acetate (MPA, 2.5 mg) (standard-dose group, n = 18),
- CEE (0.3 mg) plus MPA (2.5 mg) (low-dose group, n = 18),
- No treatment (control group, n = 15) for 3 months.

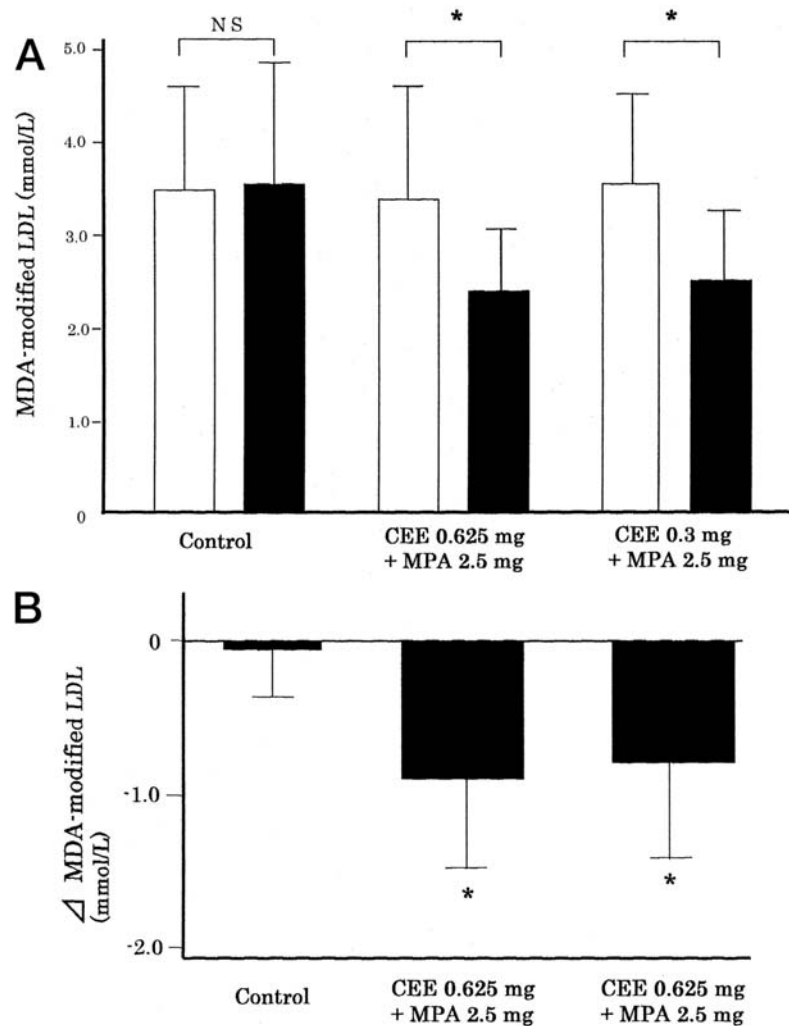
A Comparison of Low-Dose and Standard-Dose Oral Estrogen on Forearm Endothelial Function in Early Postmenopausal Women

- Outcome measures
- Lipids, Malondialdehyde (MDA) modified LDL
- Forearm Blood Flow during reactive hyperaemia (SL NG) measured by strain gauge plethysmography

A Comparison of Low-Dose and Standard-Dose Oral Estrogen on Forearm Endothelial Function in Early Postmenopausal Women

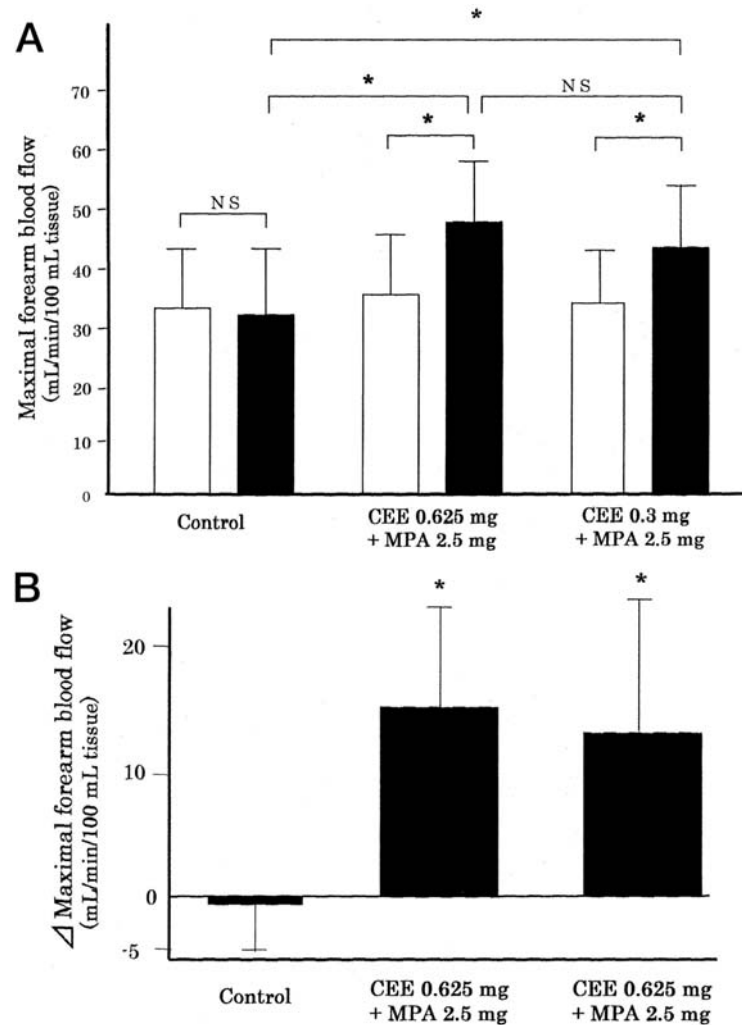
- **Results**
- Decreases in LDL, modified LDL and increase in HDL
- Similar increases in maximal FBF during reactive hyperaemia were observed in both treatment groups
- FBF in control group was unchanged

A comparison of low-dose and standard-dose oral estrogen on forearm endothelial function in early postmenopausal women.



Sanada, M. et al. J Clin Endocrinol Metab 2003;88:1303-1309

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Arterial Compliance in Older Women

- Two randomised, double-blind, placebo-controlled, cross-over studies were carried out
- Transdermal
 - 17- β estradiol alone (50mcg/24 hrs)
 - Continuous combined 17- β estradiol (50mcg/24hrs) and levonorgestrel (7mcg/24hrs)
- Active treatment/placebo for 3 months, then cross-over
- Measurement of arterial stiffness performed every 6 weeks:
 - Pulse wave velocity (Complior® system)
 - Systemic arterial compliance

Arterial Compliance in Older Women Estradiol alone

- 20 British postmenopausal women
- Mean age 70 (± 6) [1S.D]
- Mean BMI 26.8 (± 5.0)
- No differences between treatment groups for
 - Heart rate
 - Blood pressure (brachial, mean arterial, central systolic)

Arterial Compliance in Older Women Combined therapy

- 17 British women completed the study
- Mean age 58 y (range 40-65)
- After 12 weeks cCHRT, trend towards decrease in:
 - Heart rate (ns)
 - Systolic BP ($p < 0.05$)
 - Diastolic BP (ns)
 - MAP ($p = 0.06$)

Arterial Compliance in Older Women

Conclusion

- A reduction in central elastic artery stiffness was achieved following:
 - Short term transdermal estradiol alone and with continuous combined HRT SAC E2 (0.95 ± 0.6 vs 0.75 ± 0.4 , $p=0.05$)
- The reduction in central arterial stiffness by low dose transdermal E2 and E2 /levonorgestrel gives further evidence of the potentially beneficial effect of HRT on CVD risk when the appropriate dosage is used

Other Risk Markers

Effect of Lower Dose of Oral Conjugated Equine Estrogen on Size and Oxidative Susceptibility of Low-Density Lipoprotein Particles in Postmenopausal Women

- Estrogen replacement therapy (ERT) has an antioxidant effect that opposes the oxidation of LDL.
- Oral ERT-induced increases in plasma triglyceride, however, are associated with decreased LDL size, which may counteract this antioxidant effect.
- Because lower doses of oral estrogen do not affect plasma triglyceride concentrations, LDL size might not change, and the antioxidant effect of estrogen might be preserved.

Effect of Lower Dose of Oral Conjugated Equine Estrogen on Size and Oxidative Susceptibility of Low-Density Lipoprotein Particles in Postmenopausal Women

- Postmenopausal women received no treatment or were treated with oral conjugated equine estrogen (CEE) 0.625 or 0.3125 mg/d for 3 months.
- CEE at a dose of 0.625 mg/d significantly increased plasma triglyceride concentrations and decreased LDL diameter
- In contrast, 0.3125 mg of CEE did not affect plasma triglyceride concentrations or LDL diameter

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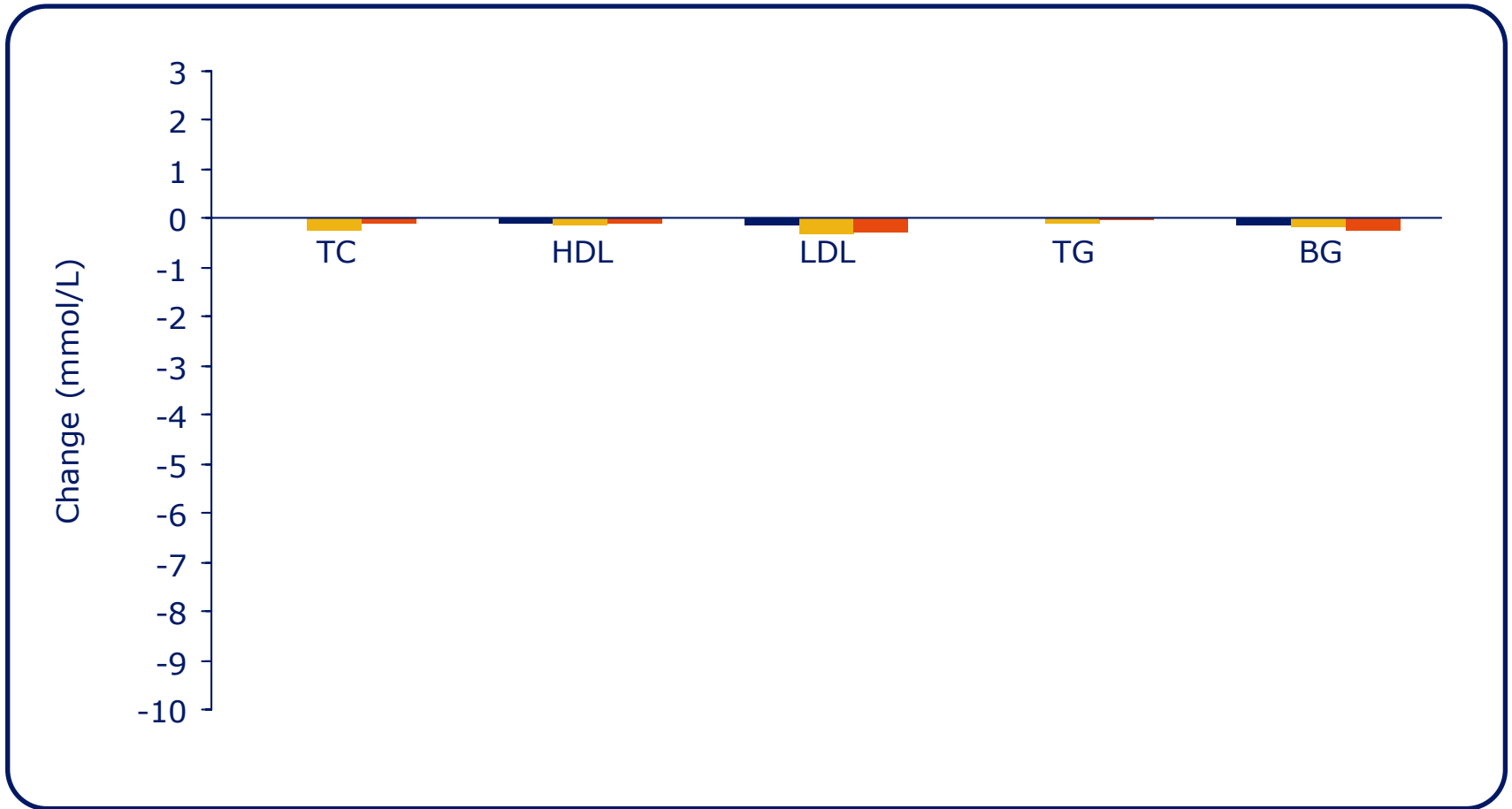
- Because oral CEE at a dose of 0.3125 mg/d does not elevate plasma triglyceride, resulting in unchanged size of LDL particles that are resistant to oxidation, the antioxidant effect of estrogen can be preserved

Ultra Low dose E2 – impact on metabolic risk factors

Clinical Study on Hormone Dose Optimisation In Climacteric Symptom Evaluation (CHOICE)

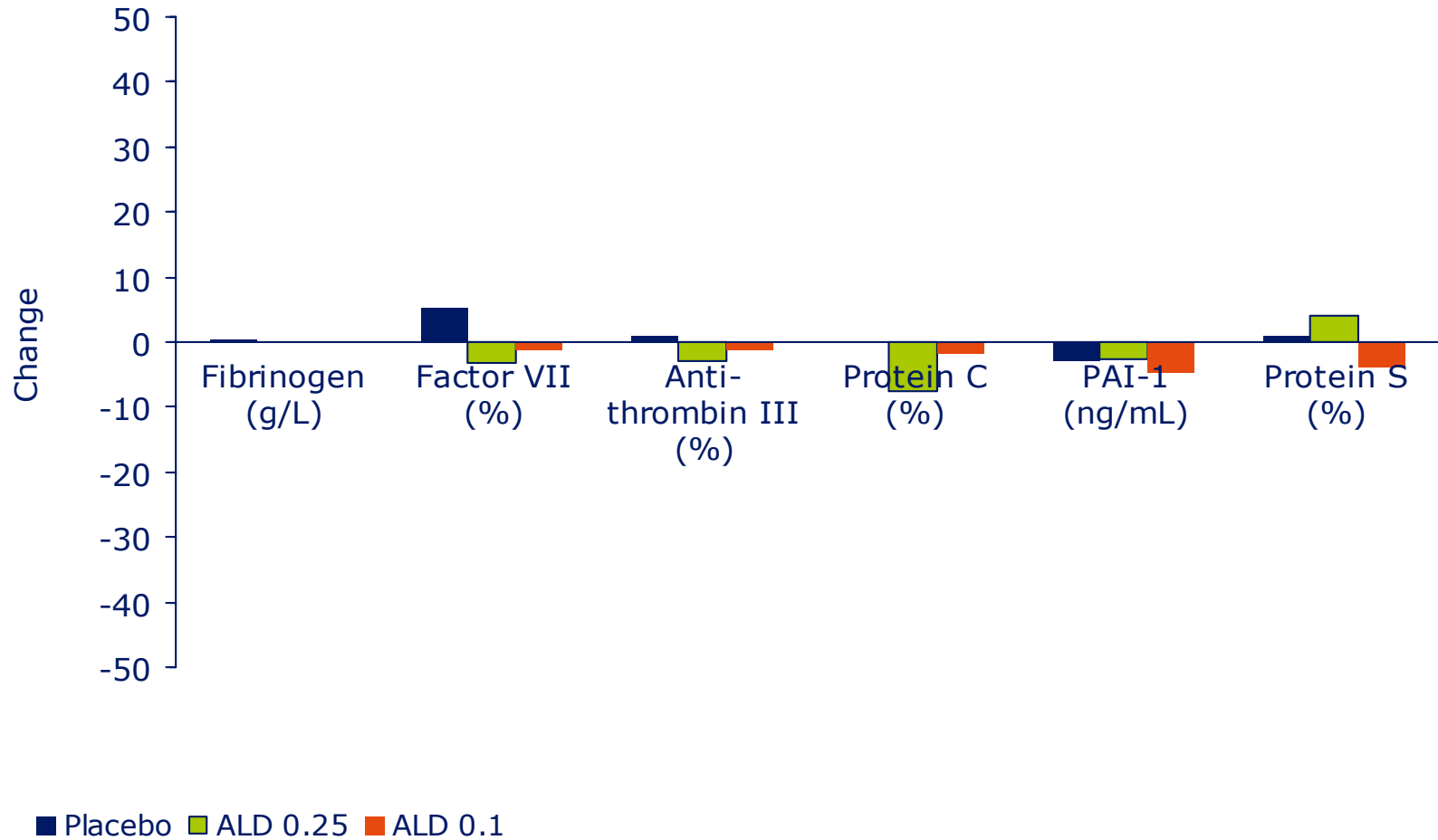
A six month double-blind, randomised, parallel-group, placebo-controlled, multi-centre trial to investigate the efficacy and safety of two ultra low dose combinations with 0.5mg estradiol and 0.1mg or 0.25mg norethisterone acetate (Activelle Low Dose (ALD) 0.1/Activelle Low Dose (ALD) 0.25) for treatment of menopausal symptoms

Metabolic parameters – change after 24 weeks therapy



■ Placebo ■ ALD 0.25 ■ ALD 0.1

Haemostasis parameters – change after 24 weeks therapy



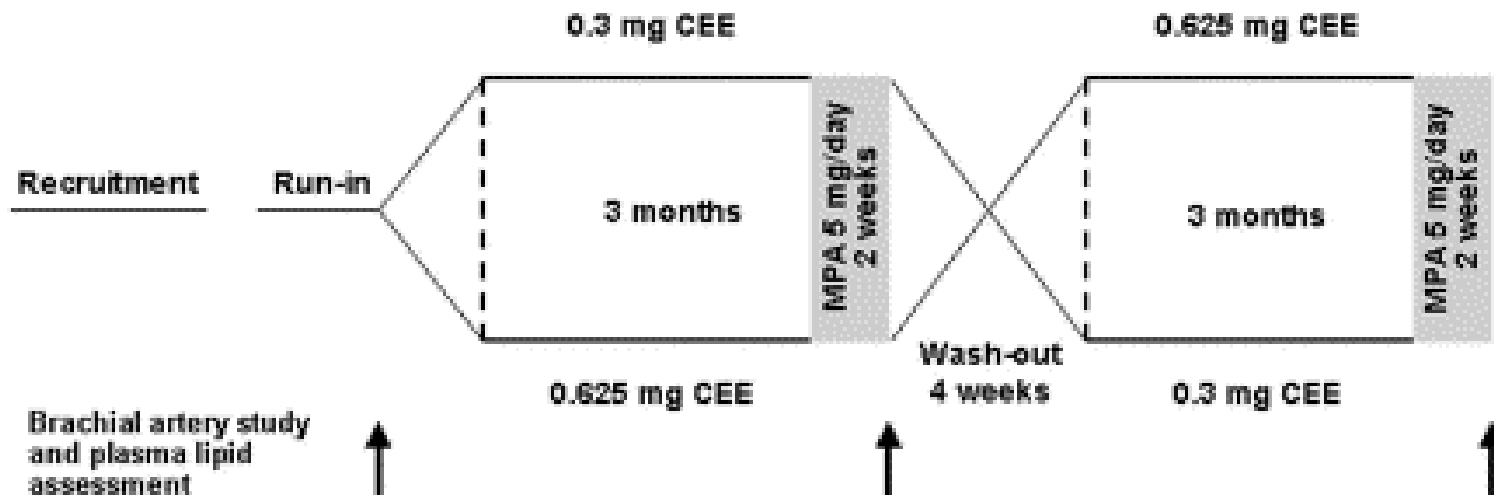
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Lipid profiles and endothelial function with low-dose hormone replacement therapy in postmenopausal women at risk for coronary artery disease: a randomized trial

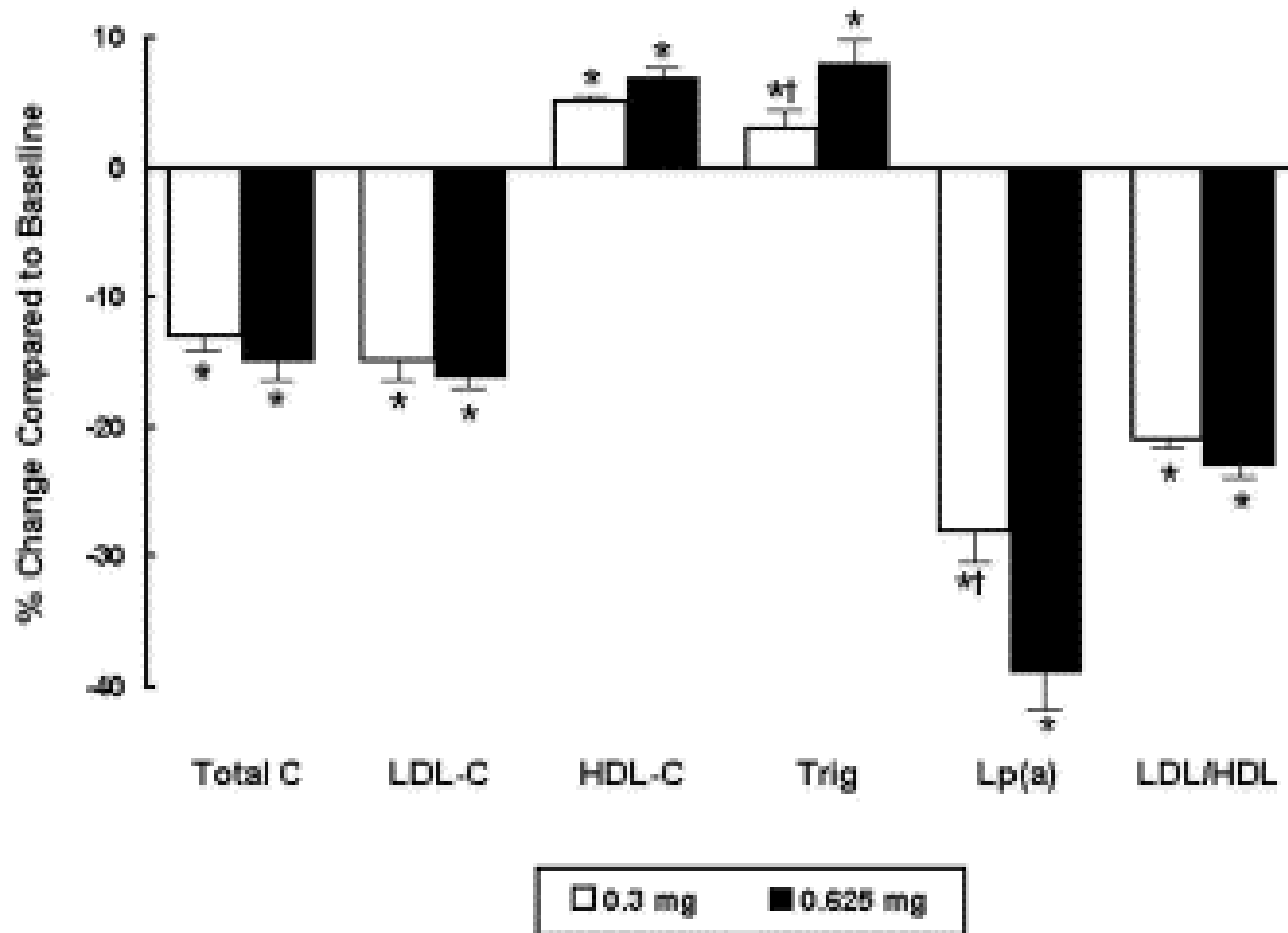
- Twenty-five Italian postmenopausal women (mean age, 65 ± 6 years) at risk for coronary artery disease (CAD) (≥ 2 established risk factors)
- Randomised double-blind study with crossover @ 12 weeks (4 weeks washout)



Lipid profiles and endothelial function with low-dose hormone replacement therapy in postmenopausal women at risk for coronary artery disease: a randomized trial

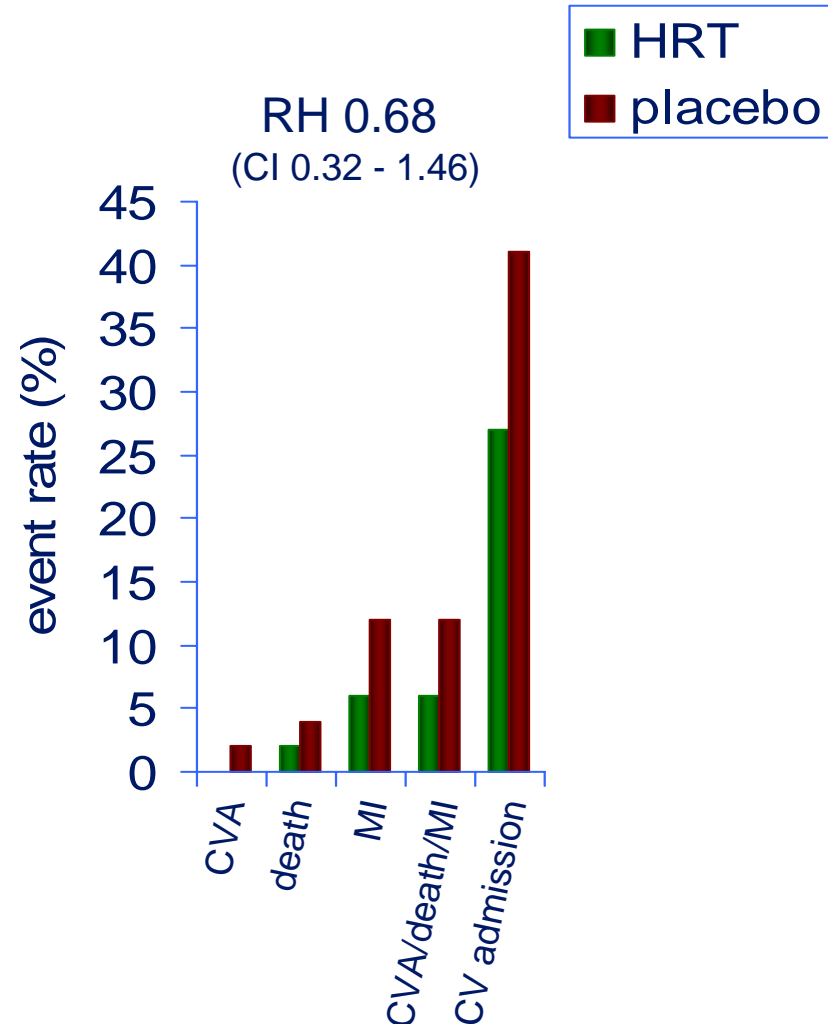
- Brachial artery endothelial function was evaluated by means of high-resolution vascular echography.
- Both CEE doses significantly improved brachial artery dilation during reactive hyperemia by 63% over baseline.
- Both doses had a favourable effect on lipids and lipoproteins – less impact of low dose on TGs
- The benefit:risk ratio of low-dose HRT provides an attractive option for postmenopausal women at risk for CAD.

Lipid profiles and endothelial function with low-dose hormone replacement therapy in postmenopausal women at risk for coronary artery disease: a randomized trial



Secondary prevention of CHD (WHISP)

- 100 postmenopausal women followed up to 12 months
- acute coronary syndrome (majority MI)
- randomised to placebo or HRT 2 - 28 days post-event
- oestradiol 17 β 1 mg/NETA 0.5 mg daily
- efficacy
 - lipid parameters
 - (clinical events)
- safety
 - haemostatic parameters



WHISP

- Low dose HRT given to older women with established CHD did not increase pro coagulant activity
- Decrease in CHD events compared with placebo
- “There is currently sufficient evidence to justify the use of HRT for symptom relief or osteoporosis prevention in women at increased risk of CHD”

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KEEPS: The Kronos Early Estrogen Prevention Study

- 42 – 58y - within 3 years of LMP
- 720 women 2005-2010
- CEE 0.45, E2 50mcg + 12 days 200mg natural progesterone
- Major Outcome Measure: Carotid Intima Media Thickness
- Secondary Measure: Coronary Calcium
- ?Pilot to 27 000 women long term prospective RCT

Conclusions

- The data from low and ultra low dose studies suggest that the benefits of higher dose preparations can be maintained whilst cardiovascular and other risks are minimised
- Effect on cardiovascular risk markers (e.g. lipids / lipoproteins / insulin resistance / arterial compliance) are either favourable or neutral
- Studies show more modest beneficial effect of low dose (0.3mg CEE) on LDL/HDL but in the absence of adverse effects on TGs and factor VII, antithrombin III and protein S

Conclusions

- Cardiovascular risk marker benefits appear to be maintained with the lower dose CEE & E2 combinations in small primary and secondary prevention trials with minimal effect on haemostatic factors
- Data look encouraging, but larger studies on major cardiovascular endpoints required to confirm beneficial impact of low dose preparations
- The low dose combinations are consistent with the advice of the regulatory authorities to prescribe the lowest effective dose

- Thank you for your attention!