**Details of the search strategy used, of the trials identified in the search and references w1- w40**

**Table A** Randomised controlled trials of hormone replacement therapy in the primary and secondary prevention of vascular disease

| Trial | Indication | No of subjects | Mean age (years) | Female (%) | Ethnicity white (%) | Uterus present (%) | Follow up (years) | Stroke rate (% of controls per year) | Intervention (daily dose) | Compliance (%) | Quality score (0-5) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Marmorston 1965[w1] | Cerebral thrombosis | 200 | 62.1 | 37 | ? | ? | ? | ? | Females: CEO (0.625 mg) Males: CEO (0.625-2.5 mg) | ? | 2 |
| Veterans Administration Cooperative 1966[w2] | Cerebrovascular disease | 592 | ? | 0 | 79.2 | ? | 1.4 | 7.72 | CEO (1.25 mg) after 1 year CEO (2.5 mg) | 94 | 5 |
| McDowell et al 1967[w3] | Non-embolic cerebral infarction | 134 | 64 | 25 | ? | ? | Treated 0.9, control 1.2 | 0 | CEO (1.25mg) | 84 | 3 |
| Nachtigall et al 1979[w4] | Hospitalised | 168 | 55.1 | 100 | 74 | ? | 10.0 | 0 | CEO (2.5 mg) + MPA (10 mg) | 88 | 4 |
| Raz et al 1993[w5] | Urinary tract infection | 93 | 65 | 100 | ? | ? | 0.7 | 0 | Estriol cream (0.5 mg) | 65 | 4 |
| Hall et al 1994[w6] | Rheumatoid arthritis | 200 | 56 | 100 | 87 | 82 | 2.0 | 0 | Transdermal O2 (50 mg) | 74 | 5 |
| PEPI 1995[w7] | Healthy | 875 | 56 | 100 | ? | 68 | 3 | 0 | CEO ± MPA or MP | 76 | 5 |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Hall et al 1998[w8] | Coronary disease | 60 | 59.4 | 100 | ? | ? | 1 | 0 | Transdermal O2 (50 mg) + MPA (5 mg) or CEO (0.625 mg) + MPA (5 mg) | 77 | 2 |
| Mijatovic et al 1998[w9] | Hysterectomy | 60 | 54.8 | 100 | ? | 100 | 2 | 0 | Raloxifene (60 mg or 150 mg) or CEO (0.625 mg) | 87 | 5 |
| Komulainen et al 1999[w10] | Healthy | 458 | 52.7 | 100 | ? | ? | 5 | 0 | E2Val (2 mg) + CPA (1 mg) | 80 | 2 |
| Ravn et al 1999[w11] | Healthy | 1 609 | 55 | 100 | 85.0 | ? | 4.0 | 0 | Alendronate (5 mg or 2.5 mg) or CEO (0.25 mg) + MPA (5 mg) | 73 | 4 |
| Recker et al 1999[w12] | Low bone mass | 128 | 72.6 | 100 | ? | ? | 3.5 | 0.45 | CEO (0.3 mg) + MPA (2.5 mg) | 61.8 | 5 |
| Høibraaten et al 2000[w13] | VTE | 140 | 56 | 100 | ? | ? | 1.3 | 1.11 | O2 (2 mg) + NTA (1 mg) | 76 | 5 |
| Mosekilde et al 2000[w14] | Healthy | 1 006 | 49.8 | 100 | ? | ? | 5 | 0.08 | O2 (2 mg) ± NA (1 mg) | 89.2 | 2 |
| Os et al 2000[w15] | Coronary artery disease | 118 | 64.5 | 100 | ? | ? | 1.0 | 0 | Transdermal O2 (50 mg) + MPA (5 mg) | 94.2 | 3 |
| Angerer et al 2001[w16] | Carotid atherosclerosis | 264 | ? | 100 | ? | ? | 1 | 0 | O2 (1 mg) + GG (0.025 mg) | 98 | 4 |
| Binder et al | Healthy | 59 | 82 | 100 | 86 | 62 | 0.75 | 0 | CEO (0.625 | 81 | 5 |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| 2001[w17] | | | | | | | | | mg) + MPA (5 mg) | | |
| Gallagher et al 2001[w18] | Healthy | 489 | 71 | 100 | 98 | 41 | 3.0 | 0.95 | CEO (0.625 mg) ± MPA (2.5 mg) | 78 | 5 |
| Hodis et al 2001[w19] | Healthy | 222 | 62 | 100 | 58 | 62 | 2.0 | 0 | O2 (1 mg) | 94 | 5 |
| Simon et al 2001[w20] | IHD | 2 763 | 67 | 100 | ? | 100 | 4.1 | 1.18 | CEO (0.625 mg) + MPA (2.5 mg) | 78 | 5 |
| Viscoli et al 2001[w21] | Stroke | 664 | 71 | 100 | ? | 55 | 2.7 | 6.34 | O2 (1 mg) | 66 | 5 |
| Arrenbrecht et al 2002[w22] | Healthy | 160 | 53 | 100 | 99 | ? | 2.0 | 0 | Transdermal O2 (100 mg or 50 mg) | 76 | 4 |
| ESPRIT 2002[w23] | MI | 1 017 | 62.3/62.9 | 100 | ? | ? | 2.0 | 0.59 | O2 (2 mg) | 53 | 5 |
| Giske et al 2002[w24] | Hysterectomy | 166 | 49.5 | 100 | ? | 0 | 2.0 | 0 | O2 (0.5 mg or 1 mg or 2 mg) | 84 | 4 |
| Waters et al 2002[w25] | IHD | 423 | 65 | 100 | ? | 41 | 2.8 | 0.67 | CEO (0.625 mg) ± MPA (2.5 mg) † | 69 | 5 |
| Wassertheil-Smoller et al 2003[w26] | Healthy | 16 608 | 63 | 100 | 84 | 100 | 5.6 | 0.24 | CEO (0.625 mg) + MPA (2.5 mg) | 60 | 5 |
| Holmberg et al 2004[w27] | Breast cancer | 345 | 55 | 100 | ? | ? | 2.1 | 0 | No specified treatment | ? | 3 |
| WHI Steering | Healthy | 10 739 | 63.6 | 100 | 75.3 | 0 | 6.8 | 0.32 | CEO (0.625 | 46.2 | 5 |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Committee 2004[w28] | | | | | | | | | mg) | | |

CEO=conjugated equine oestrogen. DG=desogestrel. O2=17ß-oestradiol. E2Val=Oestradiol valerate. CPA=cyproterone acetate. GG=gestogene. IHD=ischaemic heart disease. MI=myocardial infarction. MPA=medroxyprogesterone acetate. NG=norgestrel. NTA=northisterone acetate. VTE=venous thromboembolic. † progesterone given if no hysterectomy

**Table B** Trials excluded from the analysis

| Trial | Indication | No of subjects | Mean age (years) | Female (%) | Ethnicity white (%) | Uterus present (%) | Follow up (years) | Stroke rate (% of controls per year) | Intervention (daily dose) | Compliance (%) | Quality score (0-5) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Unreported** | | | | | | | | | | | |
| WISDOM[w29] | Healthy | 5664 | ? | 100 | ? | ? | ? | | CEO + MPA CEO | | ? |
| **Excluded** | | | | | | | | | | | |
| Lindsay et al 1976[w30] | Hysterectomy | 120 | ? | 100 | ? | 0 | 5.0 | Unable to ascertain stroke events | Mestranol (28.4 mg) | ? | 2 |
| McDonald et al 1994[w31] | Rheumatoid arthritis | 62 | 54 | 100 | ? | ? | 1.0 | Unable to ascertain stroke events | NTA (1 mg) | 71 | 4 |
| Perez-Jaraiz et al 1996[w32] | Bone loss | 104 | 50 | 100 | ? | ? | 1.0 | Unable to ascertain stroke events | Transdermal O2 (50 mg) + MPA (10 mg) | 94 | 3 |
| Kyllonen et al | Healthy | 78 | 52.6 | 100 | ? | ? | 2.0 | Unable to | O2 (2 mg) | 93 | 2 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1998[w33] | | | | | | | | ascertain stroke events | followed by O2 (2 mg) + MPA (10 mg) or O2 (2 mg) followed by O2 (2 mg) + MPA (20 mg) | | |
| De Kleijn et al 1999[w34] | Healthy | 121 | 47 | 100 | ? | 100 | 2.0 | Unable to ascertain stroke events | O2 (1.5 mg) +DG (0.15 mg), or CEO (0.625 mg) + N (0.15 mg) | ? | 5 |
| Guidozzi et al 1999[w35] | Ovarian cancer | 130 | ? | 100 | ? | ? | 4.0 | Unable to ascertain stroke events | CEO (0.625 mg) | 89 | 2 |
| Herrington et al 2000[w36] | Coronary disease | 309 | 65.8 | 100 | 81.9 | 38.8 | 3.2 | Only gives stroke/TIA together | CEO (0.625 mg), or CEO (0.625 mg + MPA (2.5 mg) | ? | 5 |
| Mulnard et al 2000[w37] | Alzheimer disease | 120 | 75.0 | 100 | ~89.0 | ~84.0 | 1.3 | Unable to ascertain stroke events | CEO (0.625 mg or 1.25 mg) | 81.0 | 4 |
| Watts et al 2000[w38] | Post-menopausal | 406 | 51.5 | 100 | ? | ? | 2.0 | Unable to ascertain stroke | CEO (0.3 mg or 0.625 mg or 1.25 mg) | ? | 3 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | events | | | |
| Clarke et al 2002[w39] | IHD | 255 | 67.0/66.3 | 100 | ? | 58.4 | 2.6 | Only gives stroke/TIA together | O2 (2.5 mg) or O2 (3 mg) + NG (4 mg) | 76.1 | 3 |
| Chang et al 2004[w40] | Menopause | 279 | 55 | 100 | 0 | ? | 1 | No control group | CEO (0.625 mg) + DG (10 mg) or MPA (5 mg) | 94.3 | 4 |

CEO=conjugated equine oestrogen. DG=desogestrel. O2=17ß-oestradiol. IHD=ischaemic heart disease. MPA=medroxyprogesterone acetate. NG=norgestrel. NTA=northisterone acetate.

## Appendix

### Search terms and strategy used

[1]—exp “Hormone replacement therapy” OR exp “Estrogen replacement therapy” OR exp “estrogens” OR “HRT” OR “ERT”

[2]—exp “Randomised controlled trials” OR exp “randomized controlled trials” OR exp “Clinical trials”

[3]—[1] AND [2]

[4]—Limit [3] to English language

[5]—Limit [3] to human

[6]—Limit [3] to (“clinical trial” OR “clinical trial phase I” OR “clinical trial phase ii” OR “clinical trial phase iii” OR “clinical trial phase iv” OR “controlled clinical trial” OR “journal article” OR “multicenter study” OR “randomized controlled trial”)

### References of trials included and excluded in the review, by year of publication

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