HORMONE REPLACEMENT THERAPY

TRIALS

TRIAL	YEAR	POPULATION	AGE	N° OF SUBJECTS	FOLLOW UP	TREATMENT	DESCRIPTION OF END-POINT	PRIMARY END-POINT	PRIMARY END-POINT HR	NOTES
		(Country)	**mean ± sd, range**	**TOTAL WOMEN**	**DURATION**			**TOTAL WOMEN**	**(CI) P**	
RUTH (Barrett-Connor et al [29])	JULY 2006	International trial with significant European component in postmenopausal women with CHD or multiple risk factors for CHD	67.5 Placebo 67.5 ± 6.7 Raloxifene 67.5 ± 6.6	10101 (Western Europe 46.3%, Eastern Europe 22.9%)	Median of 5.6 years.	PLACEBO vs. RALOXIFENE (60 mg daily)	Two primary outcomes: coronary events (i.e., death from coronary causes, myocardial infarction, or hospitalization for an acute coronary syndrome) and invasive breast cancer.	Coronary events: PLACEBO: 553 RALOXIFENE: 533 Invasive breast cancer: PLACEBO: 70 RALOXIFENE: 40	Coronary events: HR=0. 95 [95% CI: 0.84 - 1.07] P = 0.40 Invasive breast cancer: HR = 0.56 [95% CI: 0.38–0.83 P = 0.003	RALOXIFENE reduced the risk of invasive breast cancer: (benefit primarily due to a reduced risk of Estrogen-receptor–positive invasive breast cancers) and reduced the risk of clinical vertebral fractures (absolute risk reduction, 1.3 per 1000). RALOXIFENE increased risk of fatal stroke (absolute risk increase, 0.7 per 1000 woman-years) and venous thromboembolism (absolute risk increase, 1.2 per 1000 woman-years).

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RUTH (Collins et al [30])	FEB 2009	International trial with significant European component in postmenopausal women	67 With CHD Risk Factors PLACEBO: 67.50 ± 6.81 RALOXIFENE 67.27 ± 6.76 Established CHD PLACEBO 67.47 ± 6.54 RALOXIFENE 67.65 ± 6.48	TOTAL: 10101 (Western Europe 46.3%, Eastern Europe 22.9%)	Median of 5.6 years	PLACEBO vs. RALOXIFENE (60 mg/d)	Coronary end point (defined as coronary death, nonfatal MI, and hospitalized acute coronary syndrome and invasive breast cancer	Primary coronary end point: With CHD Risk Factors: PLACEBO 200 vs. RALOXIFENE 182 Established CHD: PLACEBO 353 vs. RALOXIFENE 351 Subgroups: Age <60 years PLACEBO 84 vs. RALOXIFENE 50 60 ≤ age <70 age ≥ 70	TOTAL: HR = 0.95 [95% CI: 0.84 - 1.07] Log-rank test p-value = 0.40 HR=0.91 [95% CI: 0.74 - 1.11] HR = 0.97 [95% CI: 0.83 - 1.12] HR= 0.59 [95% CI: 0.41 - 0.83] P=0.003 HR = 1.06 [95% CI: 0.88 -1.28] HR = 0.98; [95% CI: 0.82 - 1.17]	The effect of RALOXIFENE on the incidence of coronary events did not differ between women with CHD risk factors and those with established CHD ($P_{INTERACTION}$ = 0.64) The effect of raloxifene on the incidence of coronary events differed significantly by age. No difference between treatment groups in the incidence of coronary events in women ≥ 60.

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LIFT (Cummings et al [31])	AUG 2008	International trial with significant European component in women who had a bone mineral density T score of −2.5 or less at the hip or spine or a T score of −2.0 or less and radiologic evidence of a vertebral fracture. About 40% of the patients were 70 years of age or older, and 26% had already had a vertebral fracture	PLACEBO 68.2 ± 5.2 TIBOLONE 68.3 ± 5.2 (range: 60 – 85)	4538	Median of 34 months	PLACEBO vs. TIBOLONE (1.25 mg once-daily)	New vertebral fracture	New vertebral fracture: PLACEBO: 126 vs. TIBOLONE: 70	Relative Hazard = 0.55 [95% CI: 0.41 - 0.74] P <0.001	The TIBOLONE group had a decreased risk of nonvertebral fracture, a decreased risk of invasive breast cancer and colon cancer. The TIBOLONE group had an increased risk of stroke (Relative Hazard, 2.19; 95% CI, 1.14 to 4.23; P = 0.02), for which the study was stopped in February 2006

META-ANALYSIS

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Hormone therapy and cardiovascular disease: (Magliano et al [19])	JAN 2006	Meta-analysis of seven randomised controlled trials in non-hospitalised, postmenopausal women (primarily of Caucasian background)	Mean age between 62 and 71	Total 32523	Average between 2 and 6.8 years	PLACEBO vs. HORMONE THERAPY(HT);	'Hard' cardiovascular outcomes: non-fatal acute myocardial infarction (AMI); all stroke; death due to CHD; all-cause mortality.	Non-fatal AMI: overall: PLACEBO 424 HT 435 All stroke: Overall: PLACEBO 358 HT 473 CHD mortality: PLACEBO: 204 vs. HT: 209 All-cause mortality: PLACEBO 724 HT 757	Non-fatal AMI: $RR_{OVERALL}$=1.00 [95% CI: 0.88 - 1.14] All stroke: $RR_{OVERALL}$ =1.29 [95% CI:1.13 - 1.48] Stratified by age: Mean age < 65 years: RR =1.35 [95%CI: 1.14 - 1.60] Mean age ≥ 65 years: RR =1.20 [95% CI: 0.95 -1.51] Stratified by theraphy Combination therapy: RR =1.29 [95% CI: 1.06 - 1.56] Oestrogen-only RR =1.30 [95% CI:1.07 - 1.57] CHD mortality: $RR_{OVERALL}$=0.99 [95% CI: 0.82 - 1.21] All-cause mortality: $RR_{OVERALL}$=1.02 [95% CI: 0.93 - 1.13]	When the trials were stratified by age the summary relative risks for CHD mortality, non-fatal AMI and all-cause mortality was non significant. No significant differences between HT and PLACEBO when trials were stratified into combination therapy or oestrogen-only trials on: all-cause mortality, CHD deaths, non-fatal AMI

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Hormone replacement therapy and subsequent arterial and venous vascular events (Sare et al [18])	AUG 2008	Meta-analysis of 31 trials in menopausal women Thirty one trials using progesterone and/or oestrogen, and four trials of raloxifene (17699 patients included only in subgroup analysis) The trials comprised 22 in which vascular prevention was primary, 10 in patients with prior CHD, two in patients with previous stroke or TIA, and one in patients with VTE.	Between 47 and 75 (median 62.7).	44113	Between 16 weeks and 6.8 years (median 2 years).	Oestrogen and/ or Progesterone vs. (open or placebo-controlled)	One or more of cerebrovascular disease (CVD), Coronary heart disease events (CHD), Venous thromboembolism (VTE).	Cerebrovascular events (including stroke and TIA): CONTROLS 453/20433 vs. TREATMENT 581/23116 Coronary heart disease events (including myocardial infarction): CONTROLS 795/20214 vs. TREATMENT 841/22945 VTE (including pulmonary embolism, deep vein thrombosis and cerebral sinus thrombosis): CONTROLS 187/19841 vs. TREATMENT 360/22540	Cerebrovascular events Overall: OR =1.24 [95% CI: 1.03 – 1.41] P= 0.001 Stroke: OR =1.32 [95% CI: 1.14-1.53] Coronary heart disease events : OR =1.02 [95% CI: 0.90 - 1.11] P= 0.97 VTE: OR = 2.05 [95% CI: 1.44 - 2.92] P<0.0001	Also stroke severity was increased with HRT (OR=1.31, 95% CI : 1.12–1.54) The addition of progesterone to oestrogen doubled the risk of VTE.