# Hormone Replacement Therapy – the Evidence so far

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Use of hormone replacement therapy (HRT) is increasing worldwide as life expectancy increases and there is a widespread perception that HRT not only relieves menopausal symptoms but can also prevent or treat chronic diseases such as cardiovascular disease (CVD) and osteoporosis. This widespread use stands in stark contrast to the dearth of conclusive data regarding the merits and demerits of HRT. There is thus an urgent need to critically appraise the available evidence to assess the balance of benefits and risks.

Although numerous observational studies generally have supported the use of HRT, data from several recent randomized trails[1-5] have challenged the prevailing rationale for prescribing HRT for prevention of CVD and have raised the possibility that it may actually lead to short-term risk escalation.

### Short-term Effects of HRT

Regarding short-term use (<5 years) for alleviating the menopausal symptoms of vasomotor instability and urogenital atrophy, there is far less controversy when compared to that for long-term administration and the benefit / risk equation.

### Vasomotor Symptoms

There is a clear reduction in vasomotor symptoms with HRT, most studies having a duration of 12 months on an average[6]. A more recent 3 years randomized trial of estrogens and various estrogen / progestogen regimens versus placebo[7] confirmed a decrease in vasomotor symptoms of 72 to 83% at 12 months, an effect that was significantly reduced by 3 years.

### Urogenital Symptoms and Libido

With regard to the lower genital tract, most evidence of estrogen-induced benefit comes from observational and case-control studies. A recent meta-analysis has however shown effectiveness of estrogen regardless of the route of administration[8].

Alleviation of incontinence is at best uncertain. Two recent meta-analyses[9,10] have revealed a significant effect on subjective measures of symptomatology with no effect on objective measures of incontinence. In the face of inconclusive results, many clinicians use a trial treatment of estrogen for stress and urge incontinence. The Canadian Consensus on Menopause and Osteoporosis has recently stated in the recommendations that there is no objective benefit from Estrogen Replacement Therapy (ERT) in postmenopausal stress incontinence[11]. Also there is neither objective nor subjective benefit from ERT for postmenopausal urge incontinence[11].

Although there is no evidence to support a direct effect of estrogen on libido[6], estrogenization of the vagina aids vasocongestion and lubrication leading to relief of dysparunia. There is no controversy about treatment of overt dysparunia in postmenopausal women with vaginal atrophy[12].

### Psychological Symptoms

A meta-analysis concluded that estrogen was effective in alleviating depressed mood[13]. There is no evidence from randomized trials confirming that estrogen either elevates moods or treats proven depression.

### Long-term effects of HRT

Estrogen stops bone loss in early, late and elderly postmenopausal women by inhibition of bone resorption resulting in a 5 to 10% increase in bone mineral density (BMD) over 1-3 years [14-16]. When HRT is stopped, bone loss probably resumes at the same rate as after the menopause[17-19]. The fact that the reduction in fracture risk seems to be lost within five years of HRT withdrawal, irrespective of the duration of treatment, raises the issue of the optimum timing and duration of HRT[20].

Findings of several case-control and cohort studies[21-23] suggest HRT decreases the risk of hip fracture by about 30% and results of two small placebo controlled studies [24-25] done in women with osteoporosis, suggest a 50% reduction in the risk of spinal fractures. The results of a metaanalysis[25] of 13 randomized placebo controlled trials

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suggest a 33% (95% Confidence Interval 45-98) reduction in vertebral fractures, and those of a meta-analysis[26] of 22 randomized trials indicate a 27% (CI 0.56-0.94, p = 0.02) reduction in non-vertebral fractures in a pooled analysis, with a 40% reduction for hip and wrist fracture alone. There have been no large placebo controlled trials of HRT in women with osteoporosis and with incident fractures as a primary end-point; so the efficacy of postmenopausal HRT for prevention of osteoporotic fractures is much weaker than for other compounds (e.g. biphosphonates)[27].

The long-term effects of HRT on cancer and cardiovascular disease have been debated since HRT was first prescribed. The need for objective data on long-term effects prompted the setting up of randomized controlled trials (RCTs) to study cancer and cardiovascular disease as end points – HERS[1,28-30], EVTET[31], EST[32], WHI[4,33], ESPRIT-UK[34] and WISDOM[35]. Four of these trials [4,29,31,32,34], have published their results and three were halted prematurely [4,31,35]. The Women's Health Initiative [4,33] study, which received wide-spread publicity, published results for part of the trial which was stopped early. In the WHI[4] trial:

- Conjugated equine estrogens (CEE) plus medroxyprogestrone acetate (MP) were given to women with an intact uterus-stopped May, 2002.
- CEE only to hysterectomized women – ongoing and reports to be pubiished in 2005.
- Trial with CEE and MP was planned to last 8.5 years but was stopped early as the number of cases of breast cancer had reached a prespecified safety limit and overall risks exceeded benefits. The average follow up was 5.2 years.

Reviewing the four published RCTs, including over 20,000 women followed for up to 4.9 years on an average, the findings for seven major potentially fatal conditions that were primary or secondary outcomes are informative. These include cancer of the breast, endometrium and colorectum; coronary heart disease (CHD), stroke, pulmonary embolism and fracture neck femur.

Overall, for women randomized to HRT compared with placebo, there was a significant excess of breast cancer (Relative Risk 1.27; 95% CI 1.03-1.56), stroke (RR 1.27; 95% CI 1.06-1.51) and pulmonary embolism (RR 2.16; 95% CI 1.47-3.18); a significant deficit of colorectal cancer (RR 0.64; CI 0.45-0.92) and fracture neck of femur (RR 0.72; CI 0.52-0.98); but no overall significant excess or deficit for endometrial cancer (RR 0.76; 95% CI 0.45-1.31) or CHD (RR 1.11; 95% CI 0.96-1.30)[36].

Results from RCTs are similar to findings from observational studies for breast and colorectal cancer [37,38] as well as for venous thromboembolism (VTE)[39], and fracture neck femur. Increasing risk of breast cancer with duration of use in WHI study agrees with that in observational studies [38]. The WHI[4] trial is the first RCT to confirm the increased risk of invasive breast cancer, the primary outcome, with combined HRT. Risk of VTE is greatest soon after starting HRT than in later years another observational study finding corroborated.

Since the objective RCT data have confirmed previous observational data for these conditions, the evidence for a true effect is strong and unlikely to be due to bias or confounding.

When we come to the questions of CHD, our prevailing ideas of cardioprotective role of HRT receives a jolt. Many workers had argued that the lower rates of CHD among HRT users with compared with non-users, found in observational studies, did not necessarily indicate that HRT was protective[33,37,39]. It was the need for unbiased data on the incidence of heart disease that had prompted the setting up of most of the RCTs. For the first time results from HERS trial suggested an adverse effect of HRT on coronary disease in the first year after randomization[1,28]. Finding from WHI showed the same trend, although not significant[4]. One thing is certain – neither trial has shown long-term benefit for CHD.

The increased incidence of stroke among HRT is a new cause for concern. Results from previous observational studies had been inconclusive[39].

Beneficial effect from the WHI[4] trial included a decreased incidence of hip and vertebral fracture by a third and colorectal cancer by 37% in active group compared to that by placebo. The study was stopped after five years because the net level of risk was believed to outweigh the benefits. However, the overall level of risk, in all cases, is very small. For example for every 10,000 women treated with CEE and MP –

- An extra 7 women experience CHD event
- An extra 8 women experience a stroke
- An extra 8 women have VTE
- An extra 8 women have breast cancer
- In contrast, 6 fewer women will develop colorectal cancer and 5 fewer would suffer from hip fracture.

The WHI[4] trial design did not consider conditions such as gallbladder disease, diabetes, quality of life and cognitive function.

Existing trials are too small to provide reliable information on other conditions such as ovarian

cancer[40], or on cause specific mortality. As for Alzheimer's disease, the largest double blind randomized trials to date suggest that HRT does not slow its progress nor improve cognitive function[41]. HRT has little effect on quality-of-life other than menopausal symptoms[42,43].

New results on about 11,000 women randomized to unopposed estrogen versus placebo are expected from part of continuing WHI[4]. The data and conclusions for combined HRT reviewed here are, however, unlikely to change in the immediate future, even if different preparations or routes are used, as some have argued.

The ESPRIT team published results of their randomized, blinded, placebo-controlled secondary prevention trial[34]. Unopposed estradiol valerate did not reduce the overall risk of further cardiac events in postmenopausal women who had survived a myocardial infarction. Transdermal HRT patches containing 17β-estradiol have also shown no reduction in coronary heart disease[44]. The WELLHART study recently reported no significant effect on progression of atherosclerosis when 17β-estradiol was given, either alone or with medroxyprogesterone acetate, to postmenopausal women with established coronary atherosclerosis[45].

Results from WISDOM[35], which was randomizing 22,000 healthy women to similar estrogen-progestin combination as in WHI were due in 2012. This trial was also studying the effect of HRT on quality of life and cognitive function. The WISDOM trial team recently reviewed their project in light of the US experience. The UK Medical Research Council announced in October, 2002, that a decision had been taken to halt the WISDOM trial for scientific and practical reasons. The independent International Committee was concerned by the slow progress of WISDOM and considered that the results would be unlikely to show a large reduction in the incidence of coronary heart disease (the chief concern).

Very recently the Million Women Study was published in the Lancet which found that HRT increases the risk of breast cancer (relative risk 1.66) and also breast cancer mortality (1.22)[46]. Incidence was significantly increased for current users of preparations containing either estrogen only (RR 1.30 ; 95% CI 1.21-1.40, $p < 0.0001$), or estrogen-progestogen (RR 2.00 ; 95% CI 1.88-2.12, $p < 0.0001$) but the magnitude was substantially greater for estrogen-progestogen. Results varied little between specific estrogens and progestogens or their doses; or between continuous and sequential regimens. A physician would need to give combined HRT to 166 women for 5 years – or 53 women for 10 years – to see one extra case of breast cancer. This estimate has important health implications for current HRT users.

## Implications for practice

Two years ago a review article on HRT had listed two valid indications for initiating HRT[47] (a) for menopausal symptoms (short-term use) and (b) for prevention of osteoporosis (long-term use). Two years down the line the same journal had this to say: 'postmenopausal estrogen-progestogen therapy results in increased risk of disease, does not make asymptomatic women feel better and does not improve cognition. Further there is no role for HRT in the treatment of women without menopausal symptoms[48] HRT does not result in better quality of life among older women without menopausal symptoms[43]. Given the availability of other effective agents, the use of HRT for prevention or treatment of osteoporosis is not appropriate for most women. Because vasomotor symptoms are generally transient, only short-term use (for no more than two to three years) is generally needed[49].

A few months later, an editorial in Lancet takes an even harder stance[50]. The new evidence of breast cancer mortality dictates an explicit position for general practitioners – HRT should be discouraged and for women presenting with new postmenopausal health problems, general practitioners should seek alternative solutions. For postmenopausal symptoms include information giving and in some cases, a well informed decision to prescribed HRT for no longer than 3-6 months.

What about women already on HRT for reasons other than symptomatic control ? On the basis of available data, these women should be advised to stop HRT[49]. Discontinuing HRT should be suggested in as supportive a way as possible[50].

When estrogens are used for symptomatic control, using minimal dose that controls symptoms (e.g. 0.3 mg rather than 0.625 mg of conjugated estrogen) makes sense, although there are no long-term data indicating safety of lower doses[49]. For symptoms of genital atrophy alone, local estrogen or non-hormonal lubricants may be sufficient and should be considered[49].

## Conclusion

The lesson from the HRT story is that belief, no matter how sincerely held, is no substitute for proof in the form of adequately randomized clinical trials when it comes to medical interventions, especially long-term interventions that are being contemplated for widespread use in order to prevent disease. Similarly, observational or mechanistic animal models and basic research have tremendous value for the generation of hypothesis but should not be used to justify pharmacological interventions[51]. Lack of evidence of no harm (or benefit), is different from evidence of no

harm (or benefit)[52], a rule of evidence-based medicine almost completely overlooked in HRT promotion. This concept mandates testing innovations under real life conditions before final implementation. *Primum non nocere* must still be our first concern.

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