# Hormone replacement therapy

## reversal, revision and redemption

**Recent analyses of major studies have found that potential risks and side effects of HRT can be reduced by lowering doses, minimising or eliminating systemic progestogens, using non-oral routes and using HRT from near menopause.**

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Before 2002, NHMRC observational studies (Level III-2 and III-3 evidence; see the box on page 20), which were mostly of women who commenced hormone replacement therapies (HRT) near menopause for symptom control, suggested that long-term therapy conveyed cardiovascular and fracture benefit but increased the risk of breast cancer and thromboembolism. In 2002, initial results of the long-term, randomised, placebo-controlled trial of HRT (Women's Health Initiative [WHI], Level II evidence) showed that, after five years of combined oral conjugated equine oestrogen and medroxyprogesterone acetate (MPA) therapy in a relatively asymptomatic population aged 50 to 79 years that commenced therapy on average about 13 years after menopause, there was a significant reduction in fractures but no overall cardiovascular benefit and an increased occurrence of breast cancer and thromboembolism.[1]

The media reaction to this first view of the WHI data resulted in up to two-thirds of women taking HRT stopping therapy, often without medical

**IN SUMMARY**

- **Early results of the Women Health Initiative (WHI) trial showed increases in the occurrence of cardiovascular disease, breast cancer and thromboembolism in postmenopausal women taking combined oral hormone replacement therapy (HRT) but no increases in breast cancer and cardiovascular disease occurrence in those taking oestrogen-only therapy.**
- **Recent analyses of the WHI data and other randomised controlled trials have found that, although there are potential risks and side effects, these can be reduced by lowering HRT doses, minimising or eliminating systemic progestogens, using non-oral routes in some women and using HRT in symptomatic women from near menopause.**
- **A doubling in the risk of thromboembolism is still the main risk for women taking oral HRT. The absolute risk of thromboembolism is low if HRT is started near menopause and non-oral routes are used.**
- **The main indications for HRT remain the control of menopausal symptoms to improve quality of life.**
- **When HRT is initiated near menopause for symptom control, there may be additional benefits (reduced fracture and cardiovascular risk) that outweigh the risks (which are not significantly raised in women initiating therapy under 60 years of age).**
- **GPs can individualise and tailor HRT to minimise the start-up symptoms of bleeding and breast tenderness. In some women, therapy may be necessary for many years to avoid debilitating menopausal symptoms.**

consultation.[2] Various professional and non-professional bodies rather too quickly issued edicts, based on the initial results, saying that HRT should be used at the lowest dose for the shortest possible time in severely symptomatic women.[3]

Recent analyses from the WHI, other randomised controlled trials and observational and animal studies have now unified much of the HRT data and greatly changed the risk–benefit ratio for most women who commence HRT for symptom control around menopause (see the box on page 23).[4] These data suggest that there may be a therapeutic window of benefit if HRT is commenced around the time of menopause.

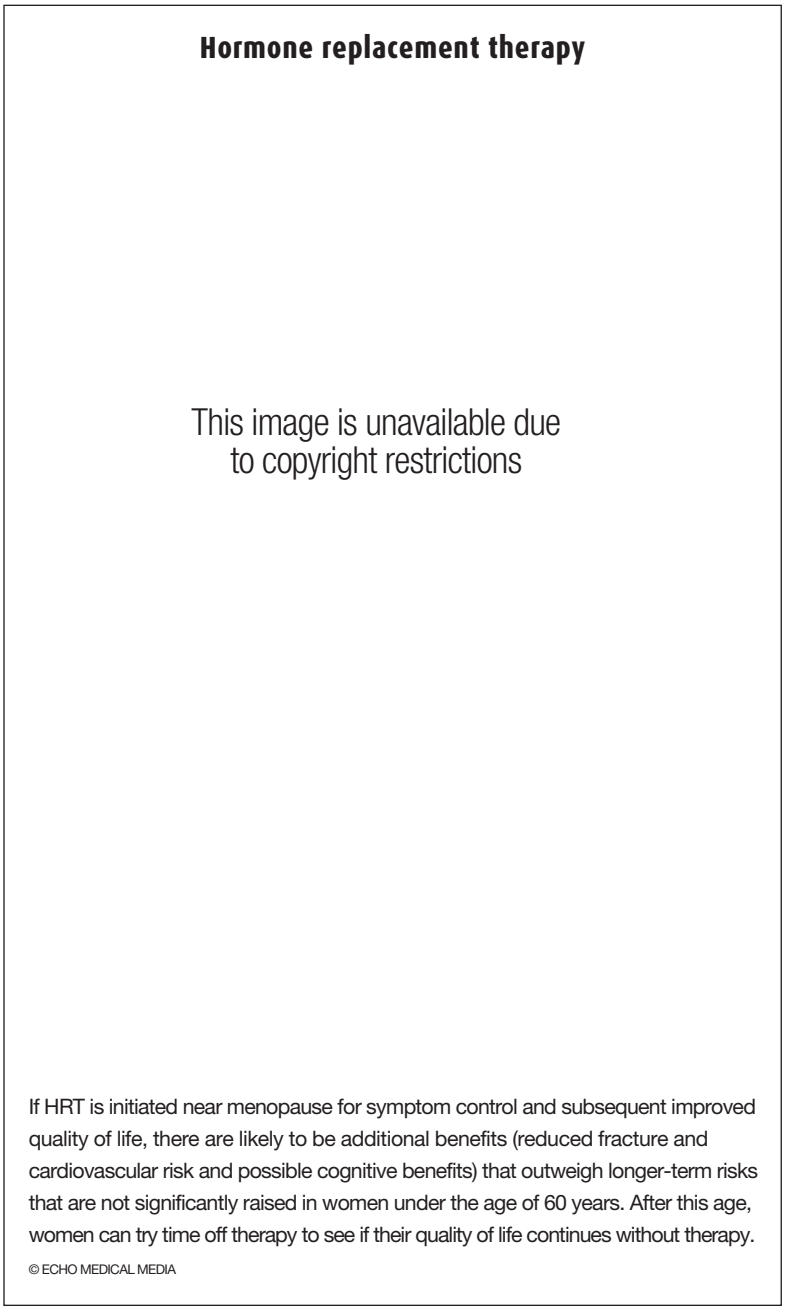
## Risks and benefits of HRT

### Cardiovascular disease

There are now increasing data in support of the 'critical therapeutic window' hypothesis that oestrogen is cardioprotective if initiated around menopause when there are still vascular oestrogen receptors responsive to exogenous HRT. This has been reviewed by myself and others.[5-7] HRT administered near menopause appears to reduce the progression of atherosclerotic plaque, but if administered many years after menopause is not beneficial and may sometimes disrupt established plaque with adverse effects. These findings have been supported by primate studies and the Heart Estrogen Replacement Study.[8,9]

A meta-analysis of clinical randomised trials (Level 1 evidence) shows a statistically and clinically significant 39% reduction in cardiac events compared with placebo control groups when HRT is initiated in women under 60 years of age (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.48–0.96), but this cardioprotective effect was not seen in older women initiating HRT after 60 years of age (OR, 1.03; 95% CI, 0.91–1.16).[10] In the WHI, which did not have the power for subgroup analysis by age, there was a nonsignificant reduction in coronary heart disease in menopausal women initiating HRT under age 60 years and in women initiating HRT within 10 years after menopause. If HRT is initiated many years after menopause, there is an increase in cardiac events during the first year of therapy (hazard ratio [HR], 1.47; 95% CI, 1.12–1.92).[10] Subsequent cardiac morbidity is reduced after two years of HRT in these older women (HR, 0.79; 95% CI, 0.67–0.93).[10] All-cause mortality in young menopausal women who take HRT compared with placebo is also significantly reduced (HR, 0.61; 95% CI, 0.39–0.95).[11] Currently, data from Level II trials in women near menopause suggest that oestrogen-only regimens may offer greater cardioprotection than some combined HRT regimens

**Hormone replacement therapy**




If HRT is initiated near menopause for symptom control and subsequent improved quality of life, there are likely to be additional benefits (reduced fracture and cardiovascular risk and possible cognitive benefits) that outweigh longer-term risks that are not significantly raised in women under the age of 60 years. After this age, women can try time off therapy to see if their quality of life continues without therapy.

**National Health and Medical Research Council levels of evidence**

| | |
|---|---|
| I | Evidence obtained from a systematic review of all relevant randomised controlled trials. |
| II | Evidence obtained from at least one properly designed randomised controlled trial. |
| III-1 | Evidence obtained from well designed pseudo-randomised controlled trials (alternate allocation or some other method). |
| III-2 | Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control analytic studies, or interrupted time series with a control group. |
| III-3 | Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group. |
| IV | Evidence obtained from case series, either post-test or pre-test and post-test. |

but more research is needed on the timing and type of progestogen therapy in combined regimens.[7,10-12]

The two long-term Level II trials of HRT (WHI and Women's International Study of long Duration Oestrogen after Menopause [WISDOM]) enrolled women who were on average 13 to 14 years postmenopause, because the outcomes being measured were more prevalent in later age. The populations in these trials were unrepresentative of symptomatic women who initiate HRT near menopause. Although the WHI alone was not powered for subanalyses of cardiac events in the 8832 women under 60 years of age in the two HRT trial arms, data from the WHI now suggest possible cardioprotection in women initiating HRT near menopause, especially when oestrogen-only regimens are used.[6,7,10,12]

A recent paper from the WHI investigators reported on atherosclerotic calcification in the coronary arteries, which is a subcomponent of atherosclerotic plaques and a marker of total plaque burden in the coronary arteries, in women in the oestrogen-only arm of the WHI trial, 8.7 years after randomisation.[13] These are markers for future possible coronary events. In women who were 80% or more compliant with oestrogen therapy (mean age, 55 years), there was 61% less atherosclerotic plaques compared with the placebo group (p=0.004).[13] Although few would yet advocate that oestrogen therapy from near menopause could be used for cardioprotection, we can now reassure women needing HRT around menopause that it is not associated with an increase in cardiac events.

## Breast cancer

Before the WHI, observational studies (Level III-2 and III-3 evidence) had suggested an increased relative risk of breast cancer with long-term combined HRT of 1.53 after a median of eight years.[14] The WHI actually reported half this risk with a relative risk after 5.6 years of combined HRT of 1.26 (adjusted 95% CI, 0.83–1.92).[1] However, some media reports highlighted the relative risk without explaining the absolute risk. The absolute increased risk of breast cancer in women taking combined HRT reported in the WHI was eight per 10,000 women-years (i.e. less than 0.1% per annum).

Systematic reviews of all the Level II and III-2 data now suggest that in women taking combined HRT, there is an increased risk of breast cancer of four per 10,000 women-years or two per 1000 women after five years.[15-17] Some groups have preferred to use worst-case scenario statistics derived from observational data including the Million Women Study (Level III-3 evidence).[18] Observational data may increase the real risk (due to selection and detection biases) and intention-to-treat analyses of randomised controlled trials may reduce the real risk due to high noncompliance rates. Both methodologies have their merits and demerits but Level II evidence is often regarded as stronger evidence than Level III-2 evidence.

Another way to look at risk is to compare the increased relative risk seen in WHI for breast cancer, which was 1.26, with other common risk factors. Thus, this relative risk is similar to the risk of breast cancer in women with late menopause at age 55 years or more (relative risk [RR], 1.22), three alcoholic drinks per day (RR, 1.4) or nulliparity (RR, 1.67).[19] Later analysis of the WHI data showed that there was no significant increase in breast cancer amongst women who initiated combined HRT for the first time during the seven years of the WHI.[20]

The oestrogen-only arm of the WHI showed a reduced rate of breast cancer of eight cases per 10,000 women-years, which did not reach significance by 7.1 years, in women who had had a hysterectomy.[21] Data on regimens that may avoid the undoubted risk of long-term combined HRT (e.g. tibolone or intrauterine progestogen and systemic oestrogen) are awaited. Observational data (Level III-3 evidence) have suggested that more than 20 years of oestrogen-only therapy may increase breast cancer rates.[22]

## Thromboembolism

Thromboembolism remains the main short-term serious risk of oral oestrogen. The risk of thromboembolism in women taking oral oestrogen appears to be greatest in the first or second year of use and is highest in those with thrombophilia and/or obesity.[23] The absolute risk varies with individual risk for thromboembolism. Risk varies with age at initiation of HRT. In the future, general screening for thrombophilia may become a cost-effective proposition. Currently, women

## Risks and benefits reported from the WHI in the oestrogen and progestogen arm and the oestrogen-only arm, compared with placebo, per 10,000 women-years[4]

Figures A and B show the overall main morbidities assessed initially in the overall WHI population who were on average 13 to 14 years post-menopause had an average age of 63 to 64 years and had a high prevalence of cardiovascular risk factors on entry to the trial. These mostly asymptomatic women were not representative of HRT users who start HRT near menopause. In contrast, recent data from the WHI allows compilation of a different morbidity profile for women in both arms of the trial who commenced HRT under 60 years of age (Figures C and D). Although the WHI was underpowered to study women under the age of 60 years (as major morbidities are uncommon in this age group), the 8832 women in WHI under 60 years of age are the largest number in a single, randomised placebo-controlled trial. Data in Figures C and D are not statistically significant.

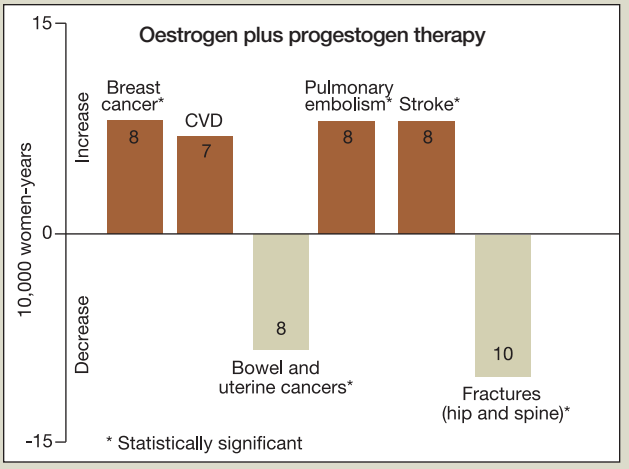



Figure A. After five years of combined HRT in women aged 50 to 79 years. Data from 16,608 women in the WHI study.

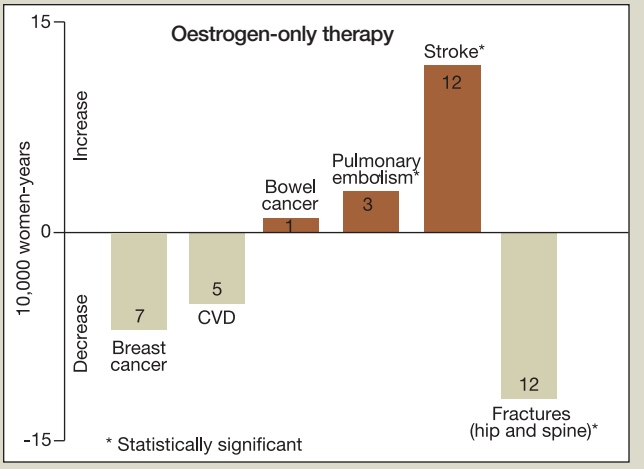



Figure B. After seven years of oestrogen-only HRT in women aged 50 to 79 years. Data from 10,739 women in the WHI study.

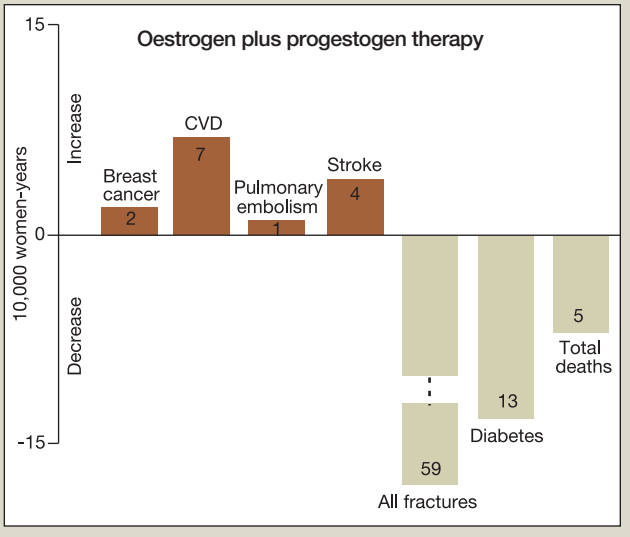



Figure C. After five years of combined HRT in women who initiated HRT under 60 years of age. Data from 5522 women in the WHI study.

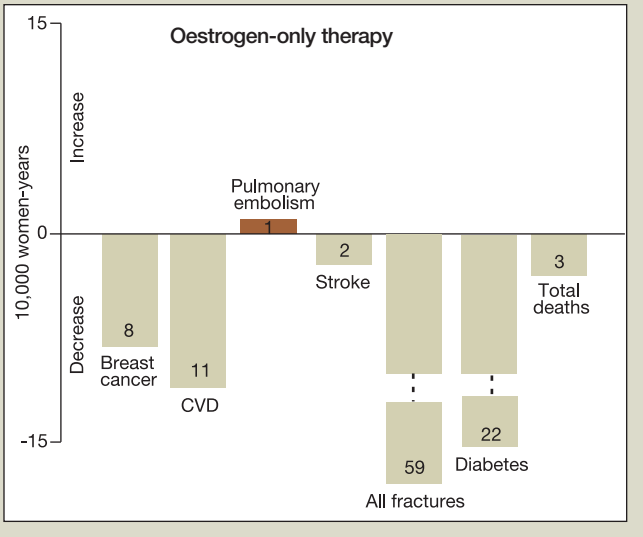



Figure D. After seven years of oestrogen-only HRT in women who initiated HRT under 60 years of age. Data from 3310 women in the WHI study.

with clinical risk factors for thromboembolism may warrant screening. Non-oral (transdermal) oestrogen, micronised progesterone and pregnane-derived progestogens have not been associated with risk of thromboembolism in women with an intact uterus (Level III-2 evidence) but no long-term randomised trials have been performed.[24]

## Fractures

The expected one-third reduction in fractures (hip, spine and overall) seen in observational studies was confirmed by WHI (combined HRT: HR, 0.76; 95% CI, 0.69–0.92; oestrogen-only therapy: HR, 0.70; 95% CI, 0.59–0.83).[1,19] Importantly, this reduction was seen in a population that was not screened for osteoporosis. HRT remains a cost efficient and relatively safe option for the prevention of fractures when initiated before 60 years of age in osteoporotic women who also have symptoms of the menopause.[25,26] Such women may have few other cost-efficient therapeutic options and this indication for HRT needs to be revisited now that the risks of HRT (especially low-dose oestrogen-only regimens) have been recalculated.

## Cognitive function and dementia

The effect of HRT on the brain is likely to remain controversial because a long-term trial starting from the time of menopause will probably be impossible. Observational studies (Level III-2 evidence) support the 'critical window hypothesis' in which use of HRT from near menopause shows more cognitive benefit than commencing HRT many years after menopause.[27] The WHI found a slight detriment in cognitive function in women commencing HRT over 65 years of age. The Cache County observational study noted a 59% reduction in dementia in women who took HRT therapy from early menopause and for more than 10 years.[28] Other Level III-3 studies, which have not distinguished between early or late initiation of HRT, have not seen consistent cognitive benefit.

## Stroke

In the WHI trial, no effect of combined HRT on stroke was seen in the first year of therapy. The risk ratios increased to 1.72 over the next four years and decreased to 0.66 in the sixth year. Yearly confidence intervals have not been published but in the elderly WHI population, the overall absolute increased risk was eight per 10,000 women-years (0.08%). The final hazard ratio for stroke was 1.31 (adjusted 95% CI, 0.93–1.84).[29] In the oestrogen-only arm of WHI, the hazard ratio was 1.39 (adjusted 95% CI, 0.97–1.99). The prevalence of stroke is age-dependent and the numbers of affected women initiating HRT under 60 years of age were small, and too small to test the critical window

hypothesis for stroke. An increased risk of transient ischaemic attacks and strokes must currently be presumed as likely in women initiating HRT many years after menopause.

### Ovarian cancer

Data from the WHI, observational studies and results from the Million Women Study show a nonsignificant increase in ovarian cancer after five years of combined HRT, but a significant increase after five years of unopposed oestrogen-only therapy.[30] The increased absolute risk in the Million Women Study was estimated as one in 2500. This risk is mostly seen in women who have had a hysterectomy with ovarian conservation and have taken oestrogen for more than five years. This group comprises about 8% of HRT users. In this group, the reduction in occurrence of breast cancer seen in the WHI trial would balance the mortality associated with both cancers. More data on HRT and possible ovarian cancer risk are needed. Tibolone (Livial) use was not associated with a rise in ovarian cancer.

### Bowel and uterine cancers

In the combined HRT arm of the WHI, a small decrease in bowel and uterine cancers was reported of around eight per 10,000 women-years.[1] Oestrogen-only therapy had no effect on bowel cancer in the WHI trial.[21]

## Early side effects of HRT

In the Cochrane systematic review of Level 1 studies of HRT for vasomotor symptoms, the only two significantly increased side effects were breast tenderness and start-up bleeding on combined continuous HRT in women with an intact uterus.[31] Breast tenderness may be transient in the first month and can usually be reversed with reduction of the oestrogen dose. Diminishing bleeding for several months is normal in women taking continuous combined regimens. This is especially so if HRT is started near the menopause and a cyclical progestogen and continuous oestrogen may be a better initial option for these patients.

## Compliance and therapy duration

The key to successful HRT and patient adherence is to tailor the therapy and to consider non-oral routes for women in whom oral oestrogen absorption may be compromised by irritable bowel syndrome, malabsorption syndromes, increased liver metabolism or drug interactions (e.g. $H_2$ antagonists and complementary medicines such as St John's wort).

Doses should be the lowest that are effective and, to avoid ongoing symptoms, length of therapy is usually for years rather than months. One option is for women to

try a period of time off HRT every four to five years, with an expectation that about half will note a loss of quality of life warranting possible recommencement of therapy. When recommencing HRT (often at half the previous dose), the risk–benefit ratio for this regimen can be explained to the woman, allowing her to make an informed decision about further therapy. Length of therapy should not be dictated by those with no clinical responsibility for the patient or understanding of her needs.

## Symptom control and quality of life

Symptom control and perceived improved quality of life are the main reason for women to commence HRT and for high continuation rates. Systematic reviews (Level 1 evidence) show that HRT efficiently controls vasomotor and urogenital symptoms in menopausal and postmenopausal women.[32,33] In the WHI trial, joint pains were significantly reduced in women taking HRT and increased on cessation of therapy. Disease-specific quality of life scores improved in symptomatic women commencing HRT and are related to improvements in sleeplessness and tiredness and an increased libido. The media scare in 2002 prompted medical review and cessation of long-term HRT in some women who had no further indication for its use. However, many more women inappropriately stopped HRT or never started therapy because of media and medical perception of the risks of HRT. Ironically, many women who experienced menopause after 2002 may have missed a therapeutic window for possible cardioprotection and possible cognitive benefit, and also suffered unnecessary menopausal symptoms, if they avoided or their advisors denied them the option of HRT.

No complementary therapy has had a greater effect than the placebo effect seen in HRT trials.[32,34] Some drugs acting on the brain (e.g. selective serotonin reuptake inhibitors) have had a moderately better effect than placebo on reducing vasomotor symptoms.[35] So-called 'bioidentical' or 'natural' unregistered hormones, individually compounded in untested doses and combinations, and often titrated with unvalidated salivary hormone assays, are mostly unassessed for efficacy or long-term safety.[36] They should not be prescribed and they exploit a regulatory loop

hole that should be closed by the Therapeutic Goods Administration.

## Tibolone therapy

Although not a traditional HRT, tibolone, a synthetic steroid with oestrogenic, progestogenic and androgenic properties, is used as an all-in-one, single dose, oral postmenopausal therapy, with a moderately effective action on menopausal and urogenital symptoms, libido and bone. Currently it has a good safety profile in short-term, randomised controlled trials (Level II evidence) with up to four years follow up.[37]

Tibolone's potential lack of breast stimulation makes it a candidate for the treatment of menopausal symptoms in women with breast cancer. However, a four-year, placebo-controlled, randomised trial in women with breast cancer (LIBERATE) has been prematurely halted after interim analyses showed that a null effect of tibolone on breast cancer will not be seen. Details of LIBERATE will be reported in mid-2008.

There is question about a small increase in the risk of stroke seen in one trial of elderly women with osteoporosis, but this result was confounded by unusually low numbers of strokes in the placebo group. Similarly, in the Million Women Study there was an association with breast cancer, which may have been confounded by the selection of women with breast cancer for tibolone therapy.[18]

## Conclusion

Although the risks of HRT were greatly inflated by some media reports and those selling alternative therapies, there are potential side effects and risks from HRT that may be reduced by tailoring the therapy to individual patients. Emerging data suggest that side effects are reduced by:

- lowering HRT doses
- minimising or eliminating systemic progestogens
- use of non-oral routes in some women
- use of HRT in symptomatic women from near menopause.

HRT can be offered to informed women for as long as they have debilitating symptoms. However, the data are not yet strong enough to advocate it for chronic disease prevention, except perhaps for osteoporosis prevention in women near menopause, with the option of other effective fracture prevention treatments at a later age.

Systematic reviews of HRT show that the two main side effects at initiation are irregular uterine bleeding, which is normal during the first few months of combined HRT, and breast tenderness when excessive oestrogen is used.[31] The latest data on HRT do not warrant the fear and ultra conservative edicts issued in 2002. Longer-term therapy is appropriate for women with prolonged symptoms who are aware of the potential risks of their regimen in their personal circumstances. It is important for women with early menopause to continue therapy at least to the average age of menopause to avoid premature osteoporosis, heart disease and dementia. Risks of HRT in these women are not likely to be increased compared with those of the same age with a natural menopause at the average age of 51 years (except for early risk of thrombosis on oral HRT). Individualised regimens can reduce the incidence of adverse outcomes.

If HRT is initiated near menopause for symptom control and subsequent improved quality of life, there are likely to be additional benefits (reduced fracture and cardiovascular risk and possible cognitive benefits) that outweigh longer-term risks that are not significantly raised under the age of 60 years. After this age, women can try 'off therapy' to see if their quality of life continues without therapy. There is no benefit from slowly ceasing HRT. However, some women have continuing debilitating symptoms even into their seventh decade and they should not be denied HRT if their therapy and risks are assessed individually and the patient understands the risks. More information for practitioners and their patients is available at the Australasian Menopause Society website (www.menopause.org.au). MT

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*A list of references is available on request to the editorial office.*

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