Hickey, Martha; Elliott, Caroline Jane; Davison, Sonia Louise
Hormone replacement therapy British Medical Journal, 2012; 344:e763.

Originally published by BMJ –
http://www.bmj.com/content/344/bmj.e763

BMJ

BMJ 2012;344:e763 doi: 10.1136/bmj.e763 (Published 16 February 2012)

PRACTICE

THERAPEUTICS

Hormone replacement therapy

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.

A 51 year old woman presents to her general practitioner with troublesome hot flushes and night sweats for the past eight months. She is sexually active and her last period was about 5 months ago. She has taken a number of over-the-counter preparations, but none have been effective. She is anxious about having hot flushes at work and exhausted from sleep disturbance. She wants advice about managing her symptoms.

What is hormone replacement therapy?

Menopause is a normal physiological event in women, occurring at a median age of 51 years. Hormone replacement therapy (HRT) contains oestrogen for relieving menopausal symptoms; for women who still have their uterus it is combined with a progestogen for endometrial protection. The oestrogen (oestradiol, oestradiol 17β, oestrone, or conjugated equine oestrogen) can be oral, intravaginal, or transdermal. The progestogen can be oral, transdermal, or delivered via an intrauterine device (Mirena, Bayer Schering). In HRT regimens the oestrogen is taken daily, with progestogen added either sequentially (cyclic regimen) or daily (continuous combined regimen) if it is needed.[1] Tibolone is an oral synthetic steroid preparation with oestrogenic, androgenic, and progestogenic actions that can also be used as HRT. Testosterone can be added to HRT, but the role of supplemental testosterone will not be covered in this case.

The key indication for HRT or tibolone is the presence of troublesome vasomotor symptoms (hot flushes and night sweats, with or without awakening). Vasomotor symptoms are normal and affect about 80% of women during the menopause transition and are severe in about 20% of these women. The duration of these symptoms varies, with a median of four years, but may continue for as many as 12 years in about 10% of women.[2] HRT may be indicated when menopausal symptoms are adversely affecting quality of life.

How well does HRT work?

HRT is currently the most effective treatment for troublesome vasomotor symptoms. A systematic review showed a significant mean reduction in the frequency of hot flushes by around 18 a week and in the severity of hot flushes by 87% compared with placebo.[3] Large randomised controlled trials have confirmed that HRT also significantly reduces fracture risk, improves vaginal dryness and sexual function, and may also improve sleep, muscle aches and pains, and quality of life in symptomatic women.[4 5] The figure⇓ provides the estimated absolute benefits from HRT use in postmenopausal women aged 50-59 years or <10 years after menopause, based on background risk in American women,[6] using data from the largest randomised controlled trial of HRT versus placebo to date (the Women's Health Initiative study)[4] and the prospective observational Nurses' Health Study.[6 7] HRT (oestrogen alone and combined) shows significant absolute benefit for the treatment of vasomotor symptoms, vaginal dryness, and fracture reduction and for the prevention of diabetes.

The relative efficacy of tibolone compared with conventional HRT is not well established. One large, multicentre randomised double blind controlled trial found that tibolone reduced hot flushes as much as low dose (1 mg) oral oestradiol in postmenopausal women aged 45-65 years. Tibolone caused less bleeding in the first three months of treatment and less breast tenderness[8] and may also improve sexual function.[9]

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Clinical indications for HRT

Current evidence based guidelines[6 10-12] advise consideration of HRT for troublesome vasomotor symptoms in perimenopausal and early postmenopausal women without contraindications and after individualised discussion of likely risks and benefits. Starting HRT in women over age 60 years is generally not recommended. For women with premature (age <40 years) or early (<45 years) menopause, current guidelines recommend HRT until aged 50 for the treatment of vasomotor symptoms and bone preservation. HRT reduces fracture risk, but increased risk of osteoporosis alone is not an indication for HRT. Similarly, although HRT may also improve mood and libido, these are not primary indications for treatment. Vaginal symptoms alone do not require systemic HRT and can be managed with local oestrogens.

How safe is HRT?

For most symptomatic women, use of HRT for ≤5 years is safe and effective. HRT is contraindicated in some women and may lead to adverse outcomes in others. There are currently no large randomised controlled trials of the benefits and harms of HRT in women around the normal age of menopause (50-59 years), which is when vasomotor symptoms are most troublesome. The figure⇓ shows the estimated risks associated with HRT use in postmenopausal women aged 50-59 years or <10 years after menopause. However, these data are derived largely from the subgroup aged 50-59 years in the Women's Health Initiative Study[4] and the Nurses' Health Study.[7] The background risk of most adverse events linked with HRT increases with age, and risks will differ according to age and current health status. Furthermore, the Women's Health Initiative study used a regimen of oral conjugated oestrogen (Premarin) (with or without medroxyprogesterone acetate) versus placebo, and it is uncertain whether other preparations and delivery systems have similar effects. The principal risks of HRT to consider are thromboembolic disease (venous thromboembolism and pulmonary embolism); stroke; cardiovascular disease; breast and endometrial cancer; and gallbladder disease.

HRT and thromboembolic disease

Oral HRT (combined oestrogen and progestogen, and oestrogen only) increases the risk of venous thromboembolism, pulmonary embolism, and stroke.[13] These risks increase with age and with other risk factors, such as obesity, previous thromboembolic disease, smoking, and immobility. In younger (<60 years) healthy women the absolute risk of thromboembolic disease is low and mortality risks from venous thromboembolism are low. The type, dose, and delivery system of both oestrogen and progestogen may influence the risk of thromboembolic disease—for example, a recent systematic review found that oral but not transdermal HRT increased the risk of venous thromboembolism.[13] In a large prospective observational study, low dose (≤1.5 mg oral, or ≤50 μg transdermal) oestradiol did not increase the incidence of venous thromboembolism in low risk populations.[14] In clinical practice, previous venous thromboembolism and high risk of venous thromboembolism are contraindications for HRT. If HRT is used by women at increased risk of thromboembolic disease, a transdermal preparation and reduced oestrogen dose are preferred. In the absence of personal or family history, screening for inherited thrombophilias is not indicated before starting HRT.[15]

HRT and stroke

Overall, HRT increases the risk of stroke.[16] Stroke risk increases with age and is rare in women under 60 years. The risk of stroke may be lower with transdermal HRT at doses of 50 μg or less,[17] but this has not been shown in randomised controlled trials. In older women (>65 years) tibolone increases the risk of stroke.[18] In clinical practice avoid HRT or tibolone in women at high risk of stroke.

HRT and cardiovascular disease

The relation between HRT and cardiovascular disease is controversial, but the timing and duration of HRT, as well as pre-existing cardiovascular disease, are likely to affect outcomes. In the estimated risks for younger women (aged 50-59 years) (figure⇓), there was no statistically significant cardiovascular risk or harm for HRT. HRT is generally avoided in older women (>60), who are more likely to have established cardiovascular disease. Subgroup analysis from larger trials suggests that starting HRT in younger postmenopausal women may have a favourable effect on cardiovascular health,[19] but the validity of this "timing hypothesis" has not yet been shown by appropriately designed studies. In those who start HRT at about age 50 years and continue beyond age 60 years the cardiovascular risks from HRT are unknown.

HRT and breast cancer

Combined HRT

Combined HRT (oestrogen plus progestogen) increases the risk of a breast cancer diagnosis or breast cancer mortality.[20] The risk of breast cancer with tibolone is not established, but large observational studies suggest an increased risk.[21] The Women's Health Initiative study reported an excess breast cancer risk attributable to combined HRT of 8 per 10 000 women a year after four to five years of use. This equates to about a 0.1% increase in breast cancer.[4] Combined HRT also increases breast density and the risk of having an abnormal mammogram.[22]

Oestrogen-only HRT

Data are conflicting over the risk of breast cancer with oestrogen-only HRT. In the Women's Health Initiative study, conjugated equine oestrogen (Premarin) did not increase the risk of breast cancer for up to seven years of use in women who had had a hysterectomy.[11 18] Most observational studies report no increased risk for up to five years of use,[6] but the large, observational Million Women Study showed an increased risk of breast cancer with oestrogen-only HRT at less than five years of use.[21] Studies are consistent in showing a greater risk of breast cancer with combined HRT than with oestrogen alone.

HRT and endometrial cancer

In women who have an intact uterus, unopposed oestrogen may lead to endometrial hyperplasia and increases the risk of endometrial cancer.[1] For this reason women who retain their uterus and use oestrogen should also take progestogen. Combined continuous HRT does not increase the risk of endometrial cancer provided that adequate duration and dose of progestogen are used, but sequential HRT may increase risk.[1] Tibolone does not increase the risk of endometrial hyperplasia or cancer.[23]

HRT and gallbladder disease

Large randomised controlled trials have shown that HRT increases the risk of cholecystitis. Observational data (the

Million Women Study) show that this risk may be reduced by using transdermal rather than oral HRT, avoiding one cholecystectomy in every 140 users.[24]

What are the precautions for HRT?

No consensus has been reached on absolute contraindications to HRT. However, on the basis of the above data, we advise avoiding or discontinuing HRT in patients with the following:

- A history of breast cancer, as HRT may increase the risk of breast cancer recurrence and of new breast cancers.[25] Tibolone also increases the risk of breast cancer recurrence.[26] Exclude breast disease and investigate any abnormalities before starting HRT. Counsel women considering HRT that it may increase their risk of an abnormal mammogram and that combined HRT may increase their risk of breast cancer after four to five years of use
- A personal history or known high risk of venous or arterial thromboembolic disease, including stroke and cardiovascular disease, as HRT may further increase risk. Tibolone increases stroke risk in older women.[18] If HRT is prescribed, a transdermal preparation with minimal oestrogen is preferred. In the absence of personal or family history, screening for inherited thrombophilias is not indicated before starting HRT[15]
- Uncontrolled hypertension.

Other conditions that require caution with use of HRT include:

- Abnormal vaginal bleeding. HRT should not be started in women with undiagnosed abnormal vaginal bleeding. Combined HRT may often cause unscheduled bleeding in the first six months of use. Persistent or new onset (after six months) unscheduled bleeding on HRT requires investigation to exclude pelvic disease
- Abnormal liver function. Avoid oral HRT products since these are metabolised in the liver
- Migraine. This does not seem to be exacerbated by HRT so migraine is not a contraindication, but low dose transdermal preparations may be preferable[27]
- History of endometrial or ovarian cancer. Seek specialist review before considering HRT
- High risk of gallbladder disease. Advise that HRT may increase this risk further, although the risk may be lower with transdermal therapy.

How cost effective is HRT?

HRT is principally a treatment for menopausal symptoms, which makes cost effectiveness difficult to measure. Modelling studies of quality of life years (QALYs) gained in the United Kingdom and the US have used data from the Women's Health Initiative study and considered fracture reduction, breast cancer, colorectal cancer, coronary heart disease, stroke, and venous thromboembolic events over five years of HRT use.[25 28] They show that HRT is cost effective in all women compared with no treatment but that the cost effectiveness was greater in those with more severe vasomotor symptoms (UK data, estimated cost per QALY gained: £580 (€700; $920) for women with an intact uterus and £205 for women who had had a hysterectomy).[28] However, this model did not include the cost of investigating abnormal uterine bleeding with HRT or additional abnormal mammograms.

How is HRT taken and monitored?

Before HRT is started

- Consider HRT in perimenopausal or recently postmenopausal symptomatic women with low risk factors for cardiovascular or thromboembolic disease.
- Consider the nature and severity of menopausal symptoms and their impact on function and quality of life, the woman's age and health status, as well as her wishes for treatment.
- It is reasonable to advise younger, healthy postmenopausal women that HRT is unlikely to increase their risk of cardiovascular disease. However, HRT is not currently indicated in women at any age for preventing or treating cardiovascular disease.[6 10-12]
- Discuss with women any modifiable risk factors for cardiovascular disease, such as alcohol, smoking, diabetes and hypertension control. Avoid prescribing HRT in women with established cardiovascular or cerebrovascular disease or at high risk of these conditions. Calculate individual risk of cardiovascular disease (www.heartfoundation.org.au/SiteCollectionDocuments/aust-cardiovascular-risk-charts.pdf (Australia); www.bhsoc.org/Cardiovascular_Risk_Prediction_Chart.stm (UK); and www.qrisk.org/lifetime).
- Consider HRT in those at high risk of fracture if there are no contraindications. Calculate fracture risk using an online tool such as FRAX (www.shef.ac.uk/FRAX) and measure bone density with bone densitometry.
- Consider whether anxiety and/or depression may be contributing to the symptom burden.[29] Somatic symptoms of menopause, such as palpitations and sleep disorder, may be difficult to distinguish from those of depression and anxiety. HRT may reduce palpitations and improve sleep and may improve mood but is not a treatment for clinical anxiety or depression.
- Individualise discussion of risk and benefit; written information is helpful. Discuss other possible management options (see "Tips for patients" box).
- Ensure breast and cervical screening are up to date and investigate any abnormal vaginal bleeding.

Starting HRT

- Available HRT preparations vary between countries and regions. In the UK see the *British National Formulary* (bnf.org/bnf/bnf/current/100039.htm) and in Australasia see the HRT equivalents guide (www.menopause.org.au/consumers/information-sheets/426-ams-guide-to-equivalent-hrt-doses) and the National Prescribing Service's website (www.nps.org.au/__data/assets/pdf_file/0019/77113/EVC_Menopause_Insert_Oct_2009.pdf).
- Use the lowest effective dose of HRT for the minimum duration to control troublesome symptoms, as advised by most current guidelines.[6 10-12]
- Perimenopausal women may need contraception.[30] In those without contraindications, combined oral contraceptive preparations will treat vasomotor symptoms and reduce fracture risk.
- No clear consensus has emerged on whether oral or transdermal therapy is first line, but transdermal may be

preferable in those with risk factors for thromboembolic disease or if oral absorption may be limited.

- Oestrogen alone should be used in women after hysterectomy. The progestogen component of HRT may be progesterone or a progestogen, which binds to the progesterone receptor. Observational studies suggest that HRT products containing a micronised progesterone or dydrogesterone may be associated with a lower risk of breast cancer, cardiovascular disease, and thromboembolic events, but adequately powered randomised controlled trials have not yet been conducted.
- In perimenopausal women consider cyclic HRT or (in women under 50 years) low dose combined oral contraceptives to minimise irregular bleeding. In women who are one to two years postmenopausal and wish to avoid bleeding, consider continuous combined HRT or tibolone.
- Ensure that you discuss the patient's expectations of effectiveness. Some women are happy to achieve a lower level of symptom reduction to minimise side effects or hormone exposure.
- Tailor the dosage and type of HRT to symptoms and possible side effects. Start with a low dose oestrogen and consider gradually increasing the dose after four to six weeks if troublesome vasomotor symptoms persist.

Monitoring HRT

- Monitor effectiveness by improvement in symptoms (blood tests are rarely useful).
- Mastalgia and irregular bleeding may respond to a reduction in oestrogen dose.
- Unscheduled bleeding in the first six months of HRT use does not need investigation, but investigate new onset or persistent bleeding to exclude pelvic disease (www.sign.ac.uk/pdf/qrg61.pdf).
- If vasomotor symptoms persist despite adequate absorption of oestradiol, investigate other causes of hot flushes or sweating.
- Review patients at least annually to evaluate indications for use, assess individuals' risk and benefit profile, and promote lifestyle interventions to reduce or prevent chronic disease.[6 10-12] HRT does not cause weight gain.
- The schedule for other screening tests such as mammography and cervical smears is not altered by HRT use.

Continuing or ceasing HRT

Base the decision on whether to advise continuation of HRT on symptoms and ongoing risks and benefits rather than a set minimum or maximum duration of therapy. Cessation of HRT leads to recurrent symptoms for up to 50% of women. Consider the potential impact of recurrent symptoms on quality of life. The risks of HRT may be related to duration of HRT use—for example, the risk of venous thromboembolism is greatest in the first year of use, but the risk of breast cancer increases with duration of use. Most guidelines recommend using HRT for up to four to five years. No clear consensus has emerged on how to discontinue HRT, and symptoms may recur regardless of whether HRT is stopped slowly or suddenly.

What are the alternatives to HRT for menopausal symptoms?

For hot flushes and night sweats

- HRT is currently the most effective treatment for vasomotor symptoms.
- Effective non-hormonal preparations include serotonin-norepinephrine reuptake inhibitors (venlafaxine and desvenlafaxine) and selective serotonin reuptake inhibitors (paroxetine, fluoxetine, citalopram, and escitalopram).[31]
- Selective serotonin reuptake inhibitors that induce CYP2D6, particularly paroxetine and fluoxetine, should be avoided in women who take tamoxifen as they may interfere with the metabolism of tamoxifen.[32]
- Gabapentin is the only non-hormonal product shown to be equally effective as low dose oestrogen for vasomotor symptoms.[33 34]
- Clonidine is mildly effective.[31]
- Relaxation therapy, mindfulness based therapies, and cognitive behaviour therapy may improve vasomotor symptoms.[31 35] A recent systematic review showed no effect for any other interventions (including acupuncture, homeopathy, vitamin E, or magnetic devices) for hot flushes after breast cancer.[31]
- Overall, data from large randomised controlled trials do not support the efficacy of black cohosh or other "natural remedies" for the treatment of hot flushes.[36]
- So called "bio-identical" hormones have not been shown to be safe or effective.[6]

For atrophic vaginitis

- Vaginal dryness can be effectively treated with topical oestrogen.[37] Vaginal oestrogens can be used safely in the long term without additional progestogens.[38]
- Non-hormonal options for atrophic vaginitis include lubricants and vaginal moisturisers, although there is little evidence to suggest they offer the sustained benefit associated with vaginal oestrogen.[9]

We thank Richard Santen and Henry Burger for their review of the manuscript and advice about the risks and benefits of HRT.

Contributors: MH produced the first draft of the manuscript and drafted the revised versions. SLD and JE contributed to further drafts of the manuscript and revisions. All authors approved the manuscript before publication. MH is the guarantor.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; MH has received research funding from AstraZeneca for consultation, funding for conference participation from Novo Nordisk (which manufactures HRT), GlaxoSmithKline, and Bayer Shering Pharma; she has also participated in research studies with Bayer Australia. SLD has received research funding from Acrux Australia. JE has received funding from Bayer and Ausio Pharmaceuticals and is on an advisory board for Pfizer; MH is funded by a Clinical Career Development Award from the National Health and Medical Research Council Australia (number 404094); no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; externally peer reviewed.

Tips for patients

- Hormone replacement therapy (or HRT) contains oestrogen to treat menopausal symptoms and, for women who have not had a hysterectomy, a progestogen to protect the uterus from cancer. Its risks and benefits have been extensively studied. HRT is a safe and effective treatment for most healthy women with symptoms who are going through the menopause at the average age (about 51 years)
- Risks and benefits of HRT will vary according to age and other health problems. Discuss with your doctor your potential risks and benefits from HRT, whether it is suitable for you, and if so, which product may be best
- HRT is the most effective treatment in reducing the number and severity of hot flushes and night sweats at menopause. It may also improve sleep, joint aches and pains, and vaginal dryness. HRT protects against fractures resulting from osteoporosis
- HRT is also recommended when menopause occurs in women younger than 45 years until aged 50 who do not have any other conditions that might mean HRT is not suitable for them
- The effects of tibolone are similar to those of HRT, but less is known about the risks and benefits of tibolone
- Other effective treatments for hot flushes and night sweats include some antidepressants and gabapentin, a drug also used for chronic pain
- Relaxation, meditation, and cognitive behavioural therapy may also be helpful
- When vaginal dryness is the main problem, only vaginal oestrogen has been proved effective, but vaginal lubricants and moisturisers may also be helpful
- Discuss with your doctor your expectations of treatment. Higher doses of HRT may be more effective in reducing symptoms of hot flushes but may also confer greater risk. Using the lowest dose for the shortest effective time is the current approach to treatment
- Discuss ongoing use of HRT yearly with your doctor. HRT does not change the usual frequency of cervical smears and mammogram screening

Patient consent not required (patient anonymised, dead, or hypothetical).

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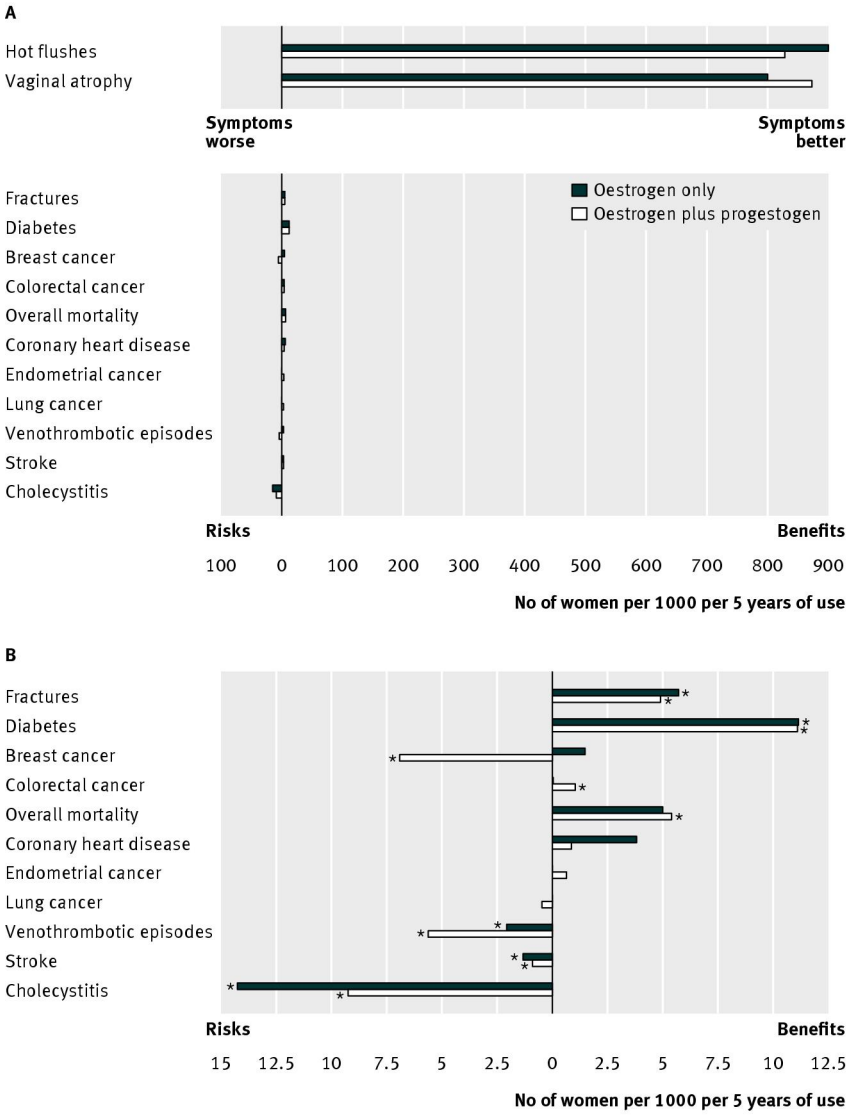
Cite this as: *BMJ* 2012;344:e763

Figure



C - Definitions of absolute and relative risks and benefits

Absolute benefit—Number of extra women per 1000 who experience a benefit attributable to HRT per 5 years of HRT use compared with those not using HRT[6]

Absolute risk—Number of extra women per 1000 who experience a risk attributable to HRT per 5 years of HRT use, compared with those not using HRT

Background risk of breast cancer, fracture, diabetes, and heart disease and overall mortality are from data on US women aged 50-59 years[6]

Relative benefits and risks associated with HRT were also derived from the subgroup of women aged 50-59 years in the Women's Health Initiative study[4] and from the Nurses' Health Study.[6,7] The following hazard ratios (95% confidence interval) were statistically significant (see panel B):
Oestrogen only (oral)—Fracture reduction 0.71 (0.64 to 0.80), diabetes reduction 0.79 (0.67 to 0.93), stroke increase 1.37 (1.09-1.73), cholecystitis increase 1.80 (1.42-2.28)
Combined (oral)—Fracture reduction 0.76 (0.69 to 0.83), diabetes reduction 0.79 (0.67 to 0.93), colorectal cancer reduction 0.61 (0.42 to 0.87), overall mortality reduction 0.69 (0.45 to 0.63), breast cancer increase 1.46 (1.22 to 1.74), stroke increase 1.31 (1.02 to 1.68), venous thromboembolic event increase 2.17 (1.57 to 2.70), cholecystitis increase 1.54 (1.22 to 1.94)

Estimated benefits and risks of oral HRT in postmenopausal women aged 50-59 years, or <10 years after menopause. Panel B shows more clearly the data in the lower part of panel A. Asterisks indicate statistically significant hazard ratios ($P<0.05$)