Managing menopause in Primary Care and recent advances in HRT

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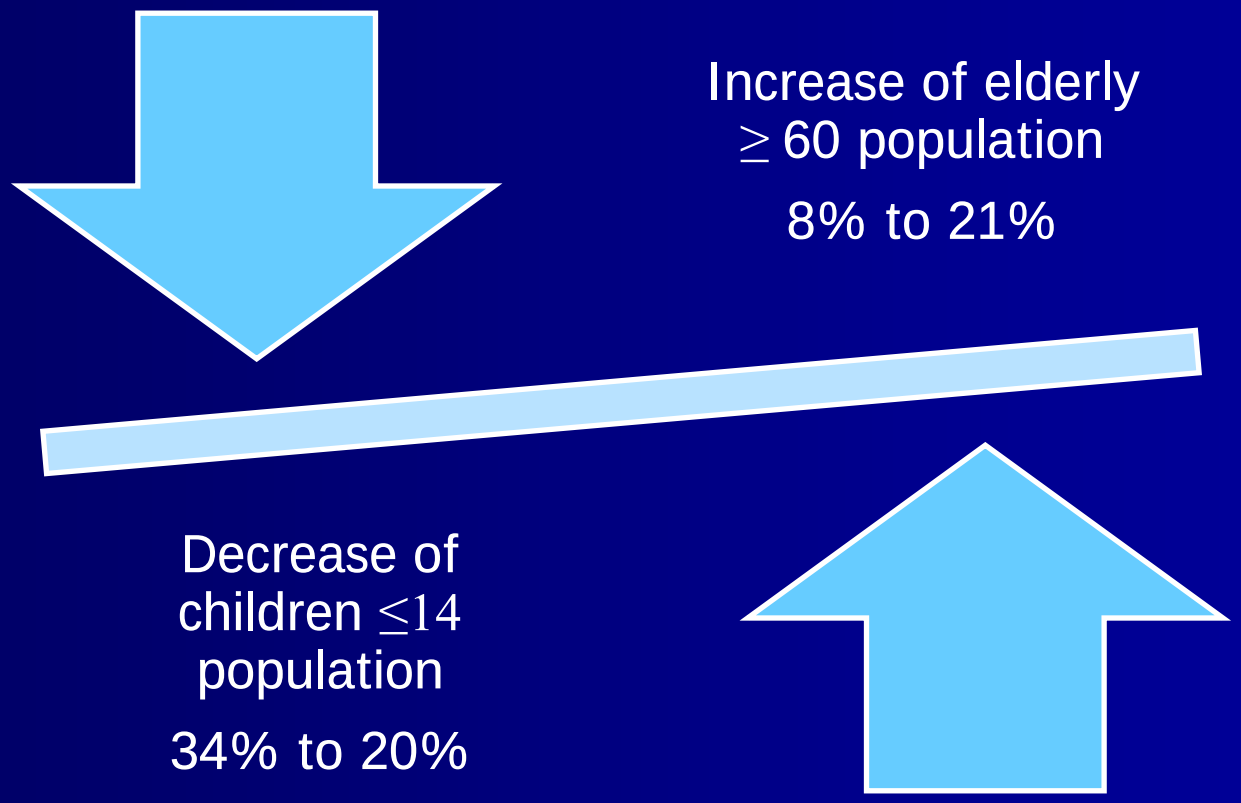
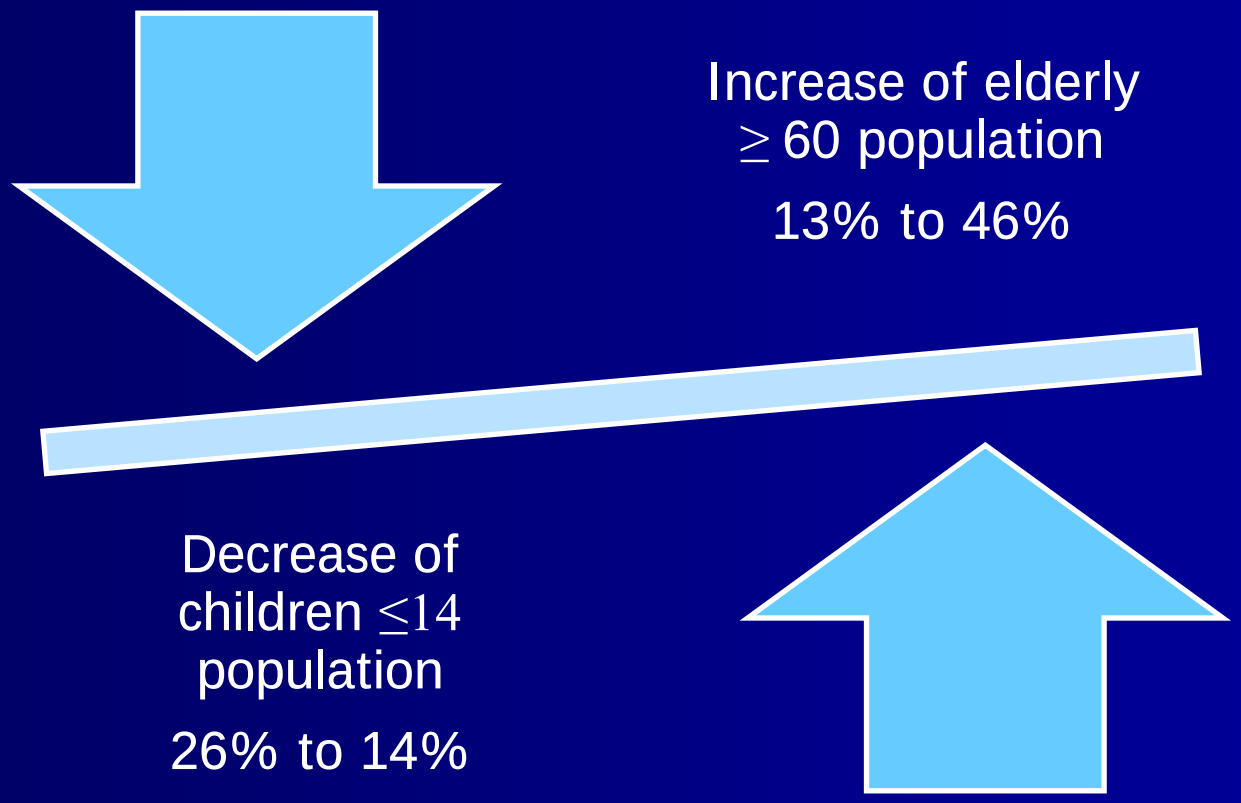
Content of today's talk

- Aims
  - To feel confident in discussing the management of menopausal symptoms with patients
  - To be able to diagnose menopause and know when it is appropriate to investigate
  - To be able to prescribe HRT safely
- Objectives
  - Review subject of menopause – why it is important?
  - Controversies and Available evidence
  - Discuss management of menopausal symptoms
  - Look in more depth at HRT preparations
  - Look at the first consultation for HRT
  - Discuss different clinical situations

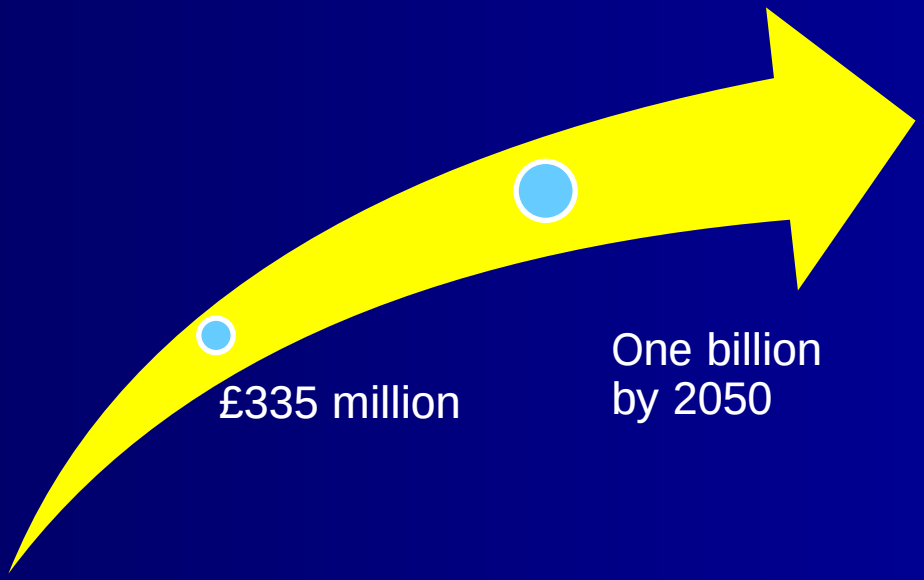
Demographic revolutions – rapidly changing population structures



Demographic revolutions – rapidly changing population structures in Europe



Elderly population by 2050
UN projection



- A large proportion of women will live in postmenopausal age

Today, women take the advent of menopause in their stride, and openly discuss their feelings:

Knowledge and scientific evidence

- Preventive measures
- Quality of life
- Social and emotional
- Activity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"Just when I thought menopause couldn't get any worse, my husband shaves off his mustache. Now, I'm the only one in the house with one."

1,000 HRT WOMEN KILLED BY CANCER

Massive study claims a deadly link

Checks . . . hot flushes are one reason for HRT

By EMMA MORTON

ONE thousand British women may have died from ovarian cancer they to shock said ye

Finding

Thousands of British women have taken HRT to relieve symptoms of the menopause. The Million Women Study, largely

16 | NEWS

Cancer risk doubles

Marilynn Marchione

TAKING menopause hormones for five years doubles the risk for breast cancer, a new analysis of a US study reveals.

Even women who took estrogen and progestin pills for just a couple of years had a greater chance of getting cancer. And when they stopped taking them, they returned to a normal risk level roughly two years after quitting.

Collectively, these new findings are likely to end any doubt that the risks outweigh the benefits for most women.

Breast cancer rates plunged in recent years mainly because millions of women quit hormone therapy and fewer newly menopausal women started on it, said the study's leader, Dr Rowan Chlebowski of Harbor-UCLA Medical Centre in Los Angeles.

"It's an excellent message for women: You can still diminish risk (by quitting), even if you've been on hormones for a long time," said Dr Claudine Isaacs of Georgetown University's Lombardi Comprehensive Cancer Centre.

"It's not like smoking, where you have to wait 10 or 15 years for the risk to come down."

Study results were given on Saturday at th Symposium in

They are fro Health Initiati estrogen and p doctors long

prevent heart disease, bone loss and other problems in women after menopause. The main part of the study was stopped in 2002 when researchers saw surprisingly higher risks of heart problems and breast cancer in hormone users.

Experts have debated

federal study were in their 60s and well past menopause.

It does change the balance on whether to start on treatment at all, Dr Chlebowski said.

Even so, most women will not get breast cancer by taking the pills short-term. The increased cancer risk from a

Review of HRT studies confirms health dangers

By Jeremy Laurance Health Editor

Friday, 20 September 2002

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Hormone replacement therapy is not a risk-free treatment for menopausal symptoms, a large-scale review of its safety has concluded.

Hormone replacement therapy is not a risk-free treatment for menopausal symptoms, a large-scale review of its safety has concluded.

Women using the treatment long term are more likely to contract a life-threatening disease than be protected against one, a study of 20,000 postmenopausal women who had taken HRT for about five years shows.

British scientists reviewed seven life-threatening conditions linked with HRT after an American trial in July showed that it increased the risk of breast cancer by 26 per cent and the risk of heart disease by 29 per cent.

Although the risk of breast cancer with HRT has been known in the last couple of years, the surprise from the American trial was the increased risk of heart disease. HRT had been thought to protect against it.

“A 51-year-old postmenopausal woman has occasional hot flushes attends your clinic to discuss HRT. She is otherwise healthy.”

Would you consider prescribing HRT?

“A 51-year-old woman has frequent and distressing hot flushes that interfere with her work and sleep, and vaginal dryness that makes sexual intercourse with her husband uncomfortable. She is otherwise healthy.”

Would you consider prescribing HRT?

Why women come to you for HRT?

They want relief from hypo-oestrogenic symptoms or they want to gain the long term benefits of HRT

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10000 person-years.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

THE WOMEN'S HEALTH INITIATIVE (WHI) focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161 809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials (trials of low-fat dietary pattern, calcium and vitamin D supplementation, and 2 trials of postmenopausal hormone use) and an observational study at 40 clinical centers in the United States.[1] This article reports principal results for the trial of combined estrogen and progestin in women with a uterus. The trial was stopped early based on health risks that exceeded health benefits over an average follow-up of 5.2 years. A parallel trial of estrogen alone in women who have had a hysterectomy is being continued, and the planned end of this trial is March 2005, by which time the average follow-up will be about 8.5 years.

The WHI clinical trials were designed in 1991-1992 using the accumulated evidence at that time. The primary outcome for the trial of estrogen plus progestin was designated as coronary heart disease (CHD). Potential cardioprotection was based on generally

For editorial comment see p 366.

Author Information and Financial Disclosures appear at the end of this article.

Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial.

The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

Table 1. Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants (N = 16 608) by Randomization Assignment*

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	*P* Value†
Age at screening, mean (SD), y	63.2 (7.1)	63.3 (7.1)	.39
Age group at screening, y			
50-59	2839 (33.4)	2683 (33.1)	.80
60-69	3853 (45.3)	3657 (45.1)	
70-79	1814 (21.3)	1762 (21.7)	
Race/ethnicity			
White	7140 (83.9)	6805 (84.0)	.33
Black	549 (6.5)	575 (7.1)	
Hispanic	472 (5.5)	416 (5.1)	
American Indian	26 (0.3)	30 (0.4)	
Asian/Pacific Islander	194 (2.3)	169 (2.1)	
Unknown	125 (1.5)	107 (1.3)	
Hormone use			
Never	6280 (73.9)	6024 (74.4)	.49
Past	1674 (19.7)	1588 (19.6)	
Current‡	548 (6.4)	487 (6.0)	
Duration of prior hormone use, y			
<5	1538 (69.1)	1467 (70.6)	.25
5-10	426 (19.1)	357 (17.2)	
≥10	262 (11.8)	253 (12.2)	
Body mass index, mean (SD), kg/m^2§	28.5 (5.8)	28.5 (5.9)	.66
Body mass index, kg/m^2			
<25	2579 (30.4)	2479 (30.8)	.89
25-29	2992 (35.3)	2834 (35.2)	
≥30	2899 (34.2)	2737 (34.0)	
Systolic BP, mean (SD), mm Hg	127.6 (17.6)	127.8 (17.5)	.51
Diastolic BP, mean (SD), mm Hg	75.6 (9.1)	75.8 (9.1)	.31

Table 2. Clinical Outcomes by Randomization Assignment*

Outcomes	No. of Patients (Annualized %) Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
Follow-up time, mean (SD), mo	62.2 (16.1)	61.2 (15.0)	NA	NA	NA
Cardiovascular disease†					
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63	0.85-1.97
CHD death	33 (0.07)	26 (0.06)	1.18	0.70-1.97	0.47-2.98
Nonfatal MI	133 (0.30)	96 (0.23)	1.32	1.02-1.72	0.82-2.13
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28	0.71-1.51
Stroke	127 (0.29)	85 (0.21)	1.41	1.07-1.85	0.86-2.31
Fatal	16 (0.04)	13 (0.03)	1.20	0.58-2.50	0.32-4.49
Nonfatal	94 (0.21)	59 (0.14)	1.50	1.09-2.08	0.83-2.70
Venous thromboembolic disease	151 (0.34)	67 (0.16)	2.11	1.58-2.82	1.26-3.55
Deep vein thrombosis	115 (0.26)	52 (0.13)	2.07	1.49-2.87	1.14-3.74
Pulmonary embolism	70 (0.16)	31 (0.08)	2.13	1.39-3.25	0.99-4.56
Total cardiovascular disease	694 (1.57)	546 (1.32)	1.22	1.09-1.36	1.06-1.40
Cancer					
Invasive breast	166 (0.38)	124 (0.30)	1.26	1.00-1.59	0.83-1.92
Endometrial	22 (0.05)	25 (0.06)	0.83	0.47-1.47	0.29-2.32
Colorectal	45 (0.10)	67 (0.16)	0.63	0.43-0.92	0.32-1.24
Total	502 (1.14)	458 (1.11)	1.03	0.90-1.17	0.86-1.22
Fractures					
Hip	44 (0.10)	62 (0.15)	0.66	0.45-0.98	0.33-1.33
Vertebral	41 (0.09)	60 (0.15)	0.66	0.44-0.98	0.32-1.34
Other osteoporotic‡	579 (1.31)	701 (1.70)	0.77	0.69-0.86	0.63-0.94
Total	650 (1.47)	788 (1.91)	0.76	0.69-0.85	0.63-0.92
Death					
Due to other causes	165 (0.37)	166 (0.40)	0.92	0.74-1.14	0.62-1.35
Total	231 (0.52)	218 (0.53)	0.98	0.82-1.18	0.70-1.37
Global index§	751 (1.70)	623 (1.51)	1.15	1.03-1.28	0.95-1.39

Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial.

Combined HRT vs Placebo

TABLE 1

Women's Health Initiative Trial Results Disease Rates (Number of Cases Per Year in 10,000 Women) for Women on Estrogen Plus Progestin or Placebo

Disease	Estrogen + Progestin	Placebo
Heart attacks	37	30
Strokes	29	21
Breast cancer	38	30
Blood clots	34	16
Colorectal cancer	10	16
Hip fractures	10	15
Endometrial cancer	5	6
Deaths	52	53

http://www.whi.org/update/2002update.asp.

Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy

The Women's Health Initiative Randomized Controlled Trial

The Women's Health Initiative Steering Committee*

Context Despite decades of use and considerable research, the role of estrogen alone in preventing chronic diseases in postmenopausal women remains uncertain.

Objective To assess the effects on major disease incidence rates of the most commonly used postmenopausal hormone therapy in the United States.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled disease prevention trial (the estrogen-alone component of the Women's Health Initiative [WHI]) conducted in 40 US clinical centers beginning in 1993. Enrolled were 10739 postmenopausal women, aged 50-79 years, with prior hysterectomy, including 23% of minority race/ethnicity.

Intervention Women were randomly assigned to receive either 0.625 mg/d of conjugated equine estrogen (CEE) or placebo.

Main Outcome Measures The primary outcome was coronary heart disease (CHD) incidence (nonfatal myocardial infarction or CHD death). Invasive breast cancer incidence was the primary safety outcome. A global index of risks and benefits, including these primary outcomes plus stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and deaths from other causes, was used for summarizing overall effects.

Results In February 2004, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided to end the intervention phase of the trial early. Estimated hazard ratios (HRs) (95% confidence intervals [CIs]) for CEE vs placebo for the major clinical outcomes available through February 29, 2004 (average follow-up 6.8 years), were: CHD, 0.91 (0.75-1.12) with 376 cases; breast cancer, 0.77 (0.59-1.01) with 218 cases; stroke, 1.39 (1.10-1.77) with 276 cases; PE, 1.34 (0.87-2.06) with 85 cases; colorectal cancer, 1.08 (0.75-1.55) with 119 cases; and hip fracture, 0.61 (0.41-0.91) with 102 cases. Corresponding results for composite outcomes were: total cardiovascular disease, 1.12 (1.01-1.24); total cancer, 0.93 (0.81-1.07); total fractures, 0.70 (0.63-0.79); total mortality, 1.04 (0.88-1.22), and the global index, 1.01 (0.91-1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10000 person-years. The estimated excess risk for all monitored events in the global index was a nonsignificant 2 events per 10000 person-years.

Conclusions The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence in postmenopausal women with prior hysterectomy over an average of 6.8 years. A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

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ESTROGEN THERAPY HAS BEEN available to postmenopausal women for more than 60 years. Proven benefits include relief of vasomotor symptoms and vaginal atrophy and prevention and treatment of osteoporosis. Observational studies primarily examining unopposed estrogen preparations have suggested a 30% to 50% reduction in coronary events,[1-3] and an 8% to 30% increase in breast cancer with extended use.[4-6]

The Women's Health Initiative (WHI) clinical trials of hormone therapy were designed in 1991-1992 using the accumulated evidence available at the time.[7] Two parallel randomized, double-blind, placebo-controlled clinical trials of hormone therapy were undertaken to determine whether conjugated equine estrogen (CEE) alone (for women with prior hysterectomy) or in combination with progestin (medroxyprogesterone acetate [MPA]) would reduce cardiovascular events in mostly healthy postmenopausal women. The WHI estrogen plus progestin trial was halted in July 2002 after a mean 5.2 years of follow-up because health risks exceeded benefits.[8] Coronary heart disease (CHD), stroke, and venous thromboembolic disease were all increased in women assigned to active treatment with estrogen plus progestin. Breast cancer was also increased while colorectal cancer, hip fracture, and other fractures were reduced. The lack of benefit for CHD was

For editorial comment see p 1769.

*Author/Steering Committee Information, Financial Disclosures, and WHI Investigators appear at the end of this article.

The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence in postmenopausal women with prior hysterectomy over an average of 6.8 years.

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A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

Table 1. Baseline Demographic and Clinical Characteristics of the Women's Health Initiative Estrogen-Alone Trial Participants With Prior Hysterectomy (N = 10 739) by Randomization Assignment*

Characteristics	CEE (n = 5310)	Placebo (n = 5429)
Age at screening, mean (SD), y	63.6 (7.3)	63.6 (7.3)
Age group at screening, y, No. (%)		
50-59	1637 (30.8)	1673 (30.8)
60-69	2387 (45.0)	2465 (45.4)
70-79	1286 (24.2)	1291 (23.8)
Race/ethnicity, No. (%)		
White	4007 (75.5)	4075 (75.1)
Black	782 (14.7)	835 (15.4)
Hispanic	322 (6.1)	333 (6.1)
American Indian	41 (0.8)	34 (0.6)
Asian/Pacific Islander	86 (1.6)	78 (1.4)
Unknown	72 (1.4)	74 (1.4)
Hormone use, No. (%)		
Never	2769 (52.2)	2770 (51.1)
Past	1871 (35.2)	1948 (35.9)
Current†	669 (12.6)	708 (13.0)
Duration of prior hormone use, y, No. (%)‡		
<5	1352 (53.2)	1412 (53.1)
5-<10	469 (18.5)	515 (19.4)
≥10	720 (28.3)	732 (27.5)
Body mass index, mean (SD)§	30.1 (6.1)	30.1 (6.2)
Body mass index, No. (%)		
<25	1110 (21.0)	1096 (20.3)
25-29	1795 (34.0)	1912 (35.5)
≥30	2376 (45.0)	2383 (44.2)

Table 3. Clinical Outcomes by Randomization Assignment

Outcomes	No. of Patients (Annualized %) CEE (n = 5310)	Placebo (n = 5429)	Hazard Ratio*	Nominal 95% CI	Adjusted 95% CI
Follow-up time, mean (SD), mo	81.6 (19.3)	81.9 (19.7)	NA	NA	NA
Cardiovascular disease†					
CHD	177 (0.49)	199 (0.54)	0.91	0.75-1.12	0.72-1.15
CHD death	54 (0.15)	59 (0.16)	0.94	0.65-1.36	0.54-1.63
Nonfatal MI	132 (0.37)	153 (0.41)	0.89	0.70-1.12	0.63-1.26
Stroke	158 (0.44)	118 (0.32)	1.39	1.10-1.77	0.97-1.99
Fatal	15 (0.04)	14 (0.04)	1.13	0.54-2.34	0.38-3.36
Nonfatal	114 (0.32)	85 (0.23)	1.39	1.05-1.84	0.91-2.12
Venous thromboembolic disease	101 (0.28)	78 (0.21)	1.33	0.99-1.79	0.86-2.08
Deep vein thrombosis	77 (0.21)	54 (0.15)	1.47	1.04-2.08	0.87-2.47
Pulmonary embolism	48 (0.13)	37 (0.10)	1.34	0.87-2.06	0.70-2.55
Total cardiovascular disease	811 (2.25)	746 (2.01)	1.12	1.01-1.24	0.97-1.30
Cancer					
Invasive breast	94 (0.26)	124 (0.33)	0.77	0.59-1.01	0.57-1.06
Colorectal	61 (0.17)	58 (0.16)	1.08	0.75-1.55	0.63-1.86
Total	372 (1.03)	408 (1.10)	0.93	0.81-1.07	0.75-1.15
Fractures					
Hip	38 (0.11)	64 (0.17)	0.61	0.41-0.91	0.33-1.11
Vertebral	39 (0.11)	64 (0.17)	0.62	0.42-0.93	0.34-1.13
Total	502 (1.39)	724 (1.95)	0.73	0.63-0.73	0.59-0.83
Death					
Due to other causes‡	193 (0.53)	185 (0.50)	1.08	0.88-1.32	0.79-1.46
Total	291 (0.81)	289 (0.78)	1.04	0.88-1.22	0.81-1.32
Global index§	502 (1.39)	705 (1.90)	1.01	0.91-1.12	0.89-1.14

Abbreviations: CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; NA, not applicable.
*From Cox proportional hazards model stratified by age, prior disease, and randomization status in the dietary modification trial.
†CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 14 silent MIs. Total cardiovascular disease is limited to events requiring or during hospitalization except venous thromboembolic disease reported after January 1, 2000.
‡All deaths except those from breast or colorectal cancer, definite/probable CHD, pulmonary embolism, or cerebrovascular disease.
§The global index represents the first event for each participant from among the following: CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, hip fracture, or death due to other causes.

Symptoms

- Hot flushes
- Palpitations
- Night sweats
- Sleep disturbances
- Vaginal dryness
- Urinary urgency
- Depressed mood
- Irritability
- Lethargy
- Forgetfulness
- Loss of concentration
- Loss of libido

To date oestrogen is the most effective treatment for hot flushes

Stages of menopausal transitions hormone levels and prevalence of hot flushes

Variable	Reproductive Years			Menopausal Transition (Perimenopause)		Postmenopausal Years	
	Early	Peak	Late	Early	Late	Early	Late
Menstrual cycle	Regular or variable	Regular		Variable cycle length; 1 or 2 missed cycles per yr	3 or more missed cycles per yr	None	
Range of steroid hormones (pg/ml)							
Estradiol	50–200			50–200 or slightly higher		40	0–15
Testosterone	400			400		400	400
Range of pituitary hormones (mU/ml)							
Follicle-stimulating hormone	10 on days 2–4			10 or higher on days 2–4		>100	
Luteinizing hormone	10 on days 2–4			10 or higher on days 2–4		>100	
Prevalence of hot flushes (%)			10	40	65	50	10–15

Strategies for hot flushes

- Estrogen is effective in 80-95%
- Non hysterectomy patient requires progesterone
- Different routes could be considered – appropriate for a particular patient
- Usually takes 4 wks to achieve substantial relief

Efficacy of different doses of estrogen and improvement of hot flushes compared to placebo

Study Group	Reduction in Frequency of Hot Flushes *percent**
Oral conjugated equine estrogens (mg)[17]	
0.625	94
0.45	78
0.30	78
Placebo	44
Oral 17β-estradiol (mg)[18]	
2.0	96
1.0	89
0.5	79
0.25	59
Placebo	55
Transdermal 17β-estradiol (mg)[19]	
0.1	96
0.05	96
0.025	86
Placebo	45

Strategies for hot flushes – non estrogenic substance

- High dose progesterone only is effective – perhaps not appropriate with current evidence
- Modest benefit on paroxetine, inconsistent result with venlafaxine
- SSRI found most effective with breast cancer
- Gabapentine was found to be modestly effective
- Clonidine is inconsistent with some side effects

Non estrogenic treatment for vasomotor symptoms

Antidepressants				
SSRIs				Extensive list of side effects[37]¶
Citalopram	30 mg	No	No benefit over placebo[33]	
Fluoxetine	20 mg	Mixed	Improvement of 24% over placebo among breast cancer survivors[34]	
	30 mg		No benefit among women without breast cancer[33]	
Paroxetine	10 to 20 mg	Yes	Improvement of 30% over placebo among breast cancer survivors[35]	
	12.5 to 25 mg CR		Improvement of 25% over placebo among women without breast cancer[36]	
Sertraline		No	No benefit over placebo among breast cancer survivors[38]	
SNRIs				
Venlafaxine	75 or 150 mg	Mixed	Improvement of 34% over placebo among breast cancer survivors[39]	Same side effects as for SSRIs, but minimal effect on cytochrome P-450 enzymes (only slightly inhibits conversion of tamoxifen to active metabolites)[41]; possible hypertension
	75 mg ER		No benefit over placebo among women without breast cancer[40]	
Gabapentin	300 mg 3 times daily	Yes	Improvement of 31% over placebo among breast cancer survivors[42] and 23% over placebo among women without breast cancer[43]	Nausea, vomiting, somnolence, dizziness, rash, ataxia, fatigue, and leukopenia
Alpha-blockers				Dry mouth, drowsiness, dizziness, hypotension, and rebound hypertension
Clonidine	0.1 mg transdermal	Mixed	Little or no benefit[4,44] or improvement of 27% over placebo[45]	
Methyldopa	375 to 1125 mg daily in divided doses	No	No benefit over placebo[4]	

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Centrally active nonhormonal hot flash therapies

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Newer antidepressants;
Nonhormonal therapies

Given the problems associated with hormonal therapy, and the prominent problem of hot flashes in menopausal women, there is a need for nonhormonal agents to alleviate hot flashes. Several compounds that appear to act on the central nervous system have been investigated. Potential mechanisms for their effects on hot flashes have been described. Bellergal (no longer available on the US market, where it was known as Bellergal-S), a combination preparation sedative that consists of low-dose phenobarbital, ergotamine tartrate, and levorotatory alkaloids of belladonna, is an old agent that was popular approximately 20 years ago; however, there is limited suggestion of efficacy for this agent. Clonidine, an older antihypertensive drug, is another centrally active agent that has been studied. Randomized trials have demonstrated that it clearly works for reducing hot flashes, but the magnitude of efficacy is somewhat limited. Toxicity from this agent limits its utility in the clinic. Methyldopa is another centrally active agent that has been studied but to a more limited degree. It appears to have minimal efficacy and too much toxicity to make it clinically useful. Anecdotal observations from a number of sources suggested that newer antidepressants can alleviate hot flashes. This led to pilot trials of venlafaxine and paroxetine, with results suggesting benefit from both drugs. Subsequently, randomized, placebo-controlled, double-blind clinical trials of venlafaxine, paroxetine, and fluoxetine were conducted. All 3 of these clinical trials demonstrated statistically significant reductions in hot flashes with these newer antidepressants compared with placebo. Pilot trials of citalopram and mirtazapine, 2 other newer antidepressants, have also suggested efficacy. Toxicity evaluations have suggested that these agents are, again, well tolerated by the majority of patients. A recent trial, however, was unable to demonstrate any benefit for fluoxetine or citalopram over a placebo. Anecdotal observations also suggested that gabapentin was helpful for alleviating hot flashes. This led to pilot trials that again suggested efficacy. Subsequently, 2 large placebo-controlled, randomized, double-blind clinical trials were conducted. Both of these demonstrated statistically significant efficacy for gabapentin compared with a placebo. This drug is relatively well tolerated by most patients. Thus, centrally active nonhormonal agents clearly do decrease hot flashes in women. The most efficacious and clinically appropriate agents for use are newer antidepressants and gabapentin. Continued evaluation of the efficacy and toxicity of these agents is ongoing.

Strategies for vaginal symptoms

- Topical estrogenic cream, tablet and ring all are very effective
- Does not raise the serum level of estrogen significantly for short term use
- Polycarbophil-based vaginal moisturiser

Alternative therapy

International Journal of Gynecology and Obstetrics 79 (2002) 195–207

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Review article

Use of alternative and complementary medicine in menopause

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Abstract

Objectives: To review the clinical evidence available for the treatment of menopausal symptoms with alternative and complementary medicine. *Methods:* The MEDLINE, PREMEDLINE and COCHRANE electronic databases for the years 1980–2002 were searched for articles concerning soy products, black cohosh, dong quai, acupuncture, ginseng and evening primrose oil. Studies pertaining to menopausal vasomotor symptoms, lipid profiles and bone mineral densities of postmenopausal women were included. The data from clinical trials were reviewed. *Results:* Soy isoflavones slightly decrease total cholesterol and LDL levels. The clinical significance of this small change is yet to be determined. The synthetic isoflavone derivative ipriflavone increases bone mineral density in healthy peri- and postmenopausal women with moderate bone mineral densities. Although earlier reports have claimed that soy is beneficial for the improvement of vasomotor symptoms, recent data do not support this claim. There are insufficient data on the other alternative therapies for treating menopausal symptoms at this time. *Conclusion:* Alternative and complementary medicine may play a role in the management of menopause, however, well-designed large studies are still needed.

Behavioural and alternative therapy

- Lowering temp.
- Regular exercise
- Breathing exercise
- Stop smoking
- No evidence in support of Acupuncture, black cohos, primrose oil, red clover
- Phytoestrogens

Different types and routes of HRT

Estrogen†	
Oral	Conjugated estrogens
	17β-Estradiol
Transdermal	17β-Estradiol
Vaginal	Estradiol acetate
Progestogen	
Oral	MPA
	Micronized progesterone
Vaginal	Progesterone
Combination preparation	
Oral sequential§	Conjugated estrogens and MPA
Oral continuous¶	Conjugated estrogens and MPA
Transdermal continuous ¶	17β-estradiol–norethindrone acetate
	17β-estradiol–levonorgestrel
	17β-estradiol–norethindrone acetate

† MPA denotes medroxyprogesterone acetate.

First consultation

- History
  - confirm menopause clinically
  - LMP
  - Symptoms
  - Gynae history – smears, mammograms
  - Risk factor for osteoporosis
  - PMH/FH breast ca/CHD/thromboembolism
  - Contraception

- Examination
  - Blood pressure
  - Height and weight
  - Breast exam?

Contd. First consultation

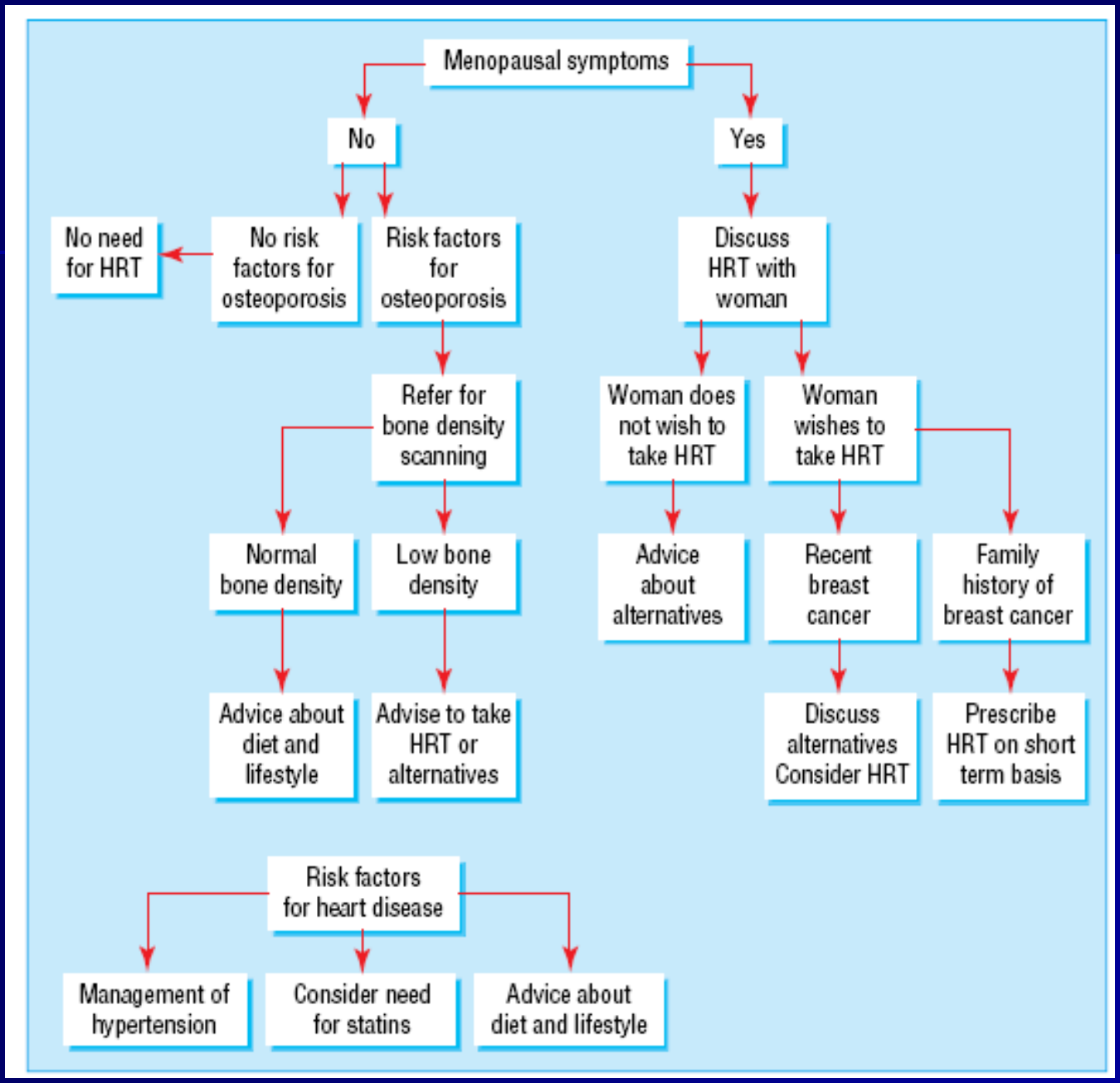
- Depression, anxiety, effect on life
- Investigations? – Any blood test or scan?
- Management
  - Lifestyle changes
  - If starting HRT
    - Discuss benefits, risks, side effects
    - Any contraindication?
    - Discuss different preparation
    - Discuss contraception
  - Alternatives
- Safety netting – investigate PCB, bleeding 1 year after LMP
- Arrange follow up

What should you do during follow up

- Reassess after 3 months then annually
- Follow up consultations should cover;
  - How effective has been the primary management?
  - Enquiring about side effects
  - Enquire about bleeding pattern any abnormal bleeding?
  - Check weight and BP
  - Ensure she examines her breasts regularly
- If on cyclical treatment, consider changing to continuous if she is considered to be postmenopausal > 1yr. This is usually considered to be
  - If she has previous raised FSH levels on two occasions or amenorrhoea > 1yr
  - If she has been on cyclical regimes for at least 2 years

Management for the woman in question?

- Inform vasomotor symptoms usually improve in few years
- Vaginal symptoms may not improve spontaneously
- Behavioural measures may not help
- HRT is most effective – has side effects
- Non hormonal therapy
- Life style change – role of calcium+D3



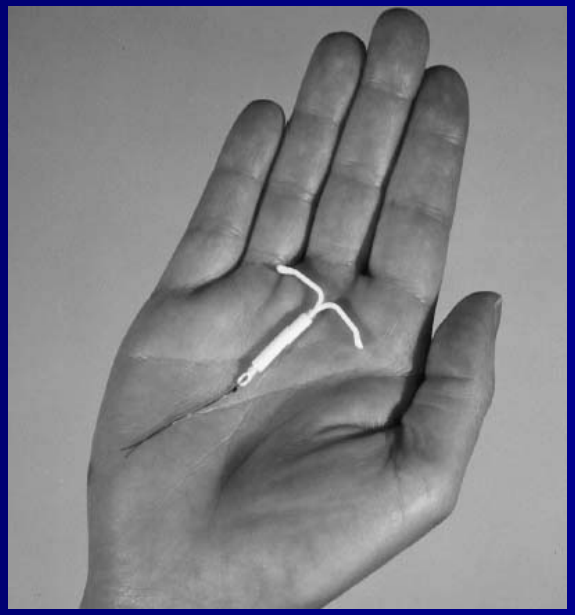
Ref: BMJ – Rymer et al

Royal College of Physicians guidance on risk factors for osteoporosis

- · Premature menopause (before the age of 40)
- · Family history of osteoporosis
- · Taken steroids for more than 6 months
- · Premenopausal amenorrhoea for more than
- 6 months (due to low body mass index or excessive
- exercise)
- · Liver, thyroid, or renal disease
- · History of excessive alcohol intake
- · Taken gonadotrophin agonists

Strategies for women prone to develop osteoporosis

- To offer bone density scan (DEXA)
- Consider biphosphonates and/or HRT
- Supplement - Calcium and Vitamin D3
- Role of Raloxifene (SERM)
- Life style changes – regular exercise, cessation of smoking



Levonorgestrel 20 micrograms/24 hours

Special situation

- Thromboembolic disease
- Cardiovascular disease
- Breast cancer
- Endometrial cancer
- Ovarian cancer
- Cervical cancer

HRT Risk

HRT Risk

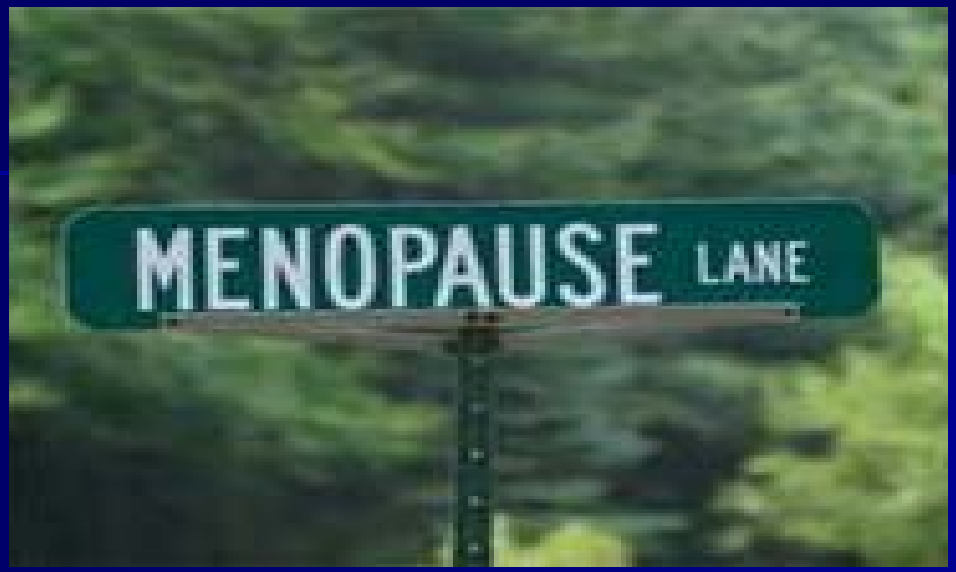
Risk	Age range (years)	Background incidence per 1000 women in Europe not using HRT		**Additional** cases per 1000 women using **oestrogen only HRT** (estimated)		**Additional** cases per 1000 women using **combined (oestrogen-progestogen) HRT** (estimated)	
		Over 5 years	Over 10 years	For 5 years' use	For 10 years' use	For 5 years' use	For 10 years' use
Breast cancer[1]	50–59	10	20	2	6	6	24
	60–69	15	30	3	9	9	36
Endometrial cancer[2][3]	50–59	2	4	4	32	NS	NS
	60–69	3	6	6	48	NS	NS
Ovarian cancer	50–59	2	4	<1	1	<1	1
	60–69	3	6	<1	2	<1	2
Venous thromboembolism[4][5]	50–59	5		2		7	
	60–69	8		2		10	
Stroke[6]	50–59	4		1		1	
	60–69	9		3		3	
Coronary heart disease [7][8]	70–79	29–44		NS		15	

Note Where background incidence or additional cases have not been included in the table, this indicates a lack of available data. NS indicates a non-significant difference

Taken from MHRA/CHM (*Drug Safety Update* 2007; **1** (2): 2–6) available at www.mhra.gov.uk/drugsafetyupdate

Alternative medicine

- They are often not regulated by a governing body.
- General rule is to advise against herbal medications.
- Many may contain estrogenic compounds.
- Women may be taking more hormones by using these than they would with HRT.
- Some studies suggest diet high in soy and isoflavones reduces severity and frequency of symptoms. They are safe.
- Acupuncture – no evidence
- Foot massage, reflexology – no evidence
- Evening primrose oil – no evidence
- Black Cohosh – limited evidence
- Red Clover – limited evidence, no health concerns
- Dong Quai – no evidence



It is a beginning of a journey

Understanding, knowledge and joint co-operation

Thank you