MENOPAUSE
AN UPDATE ON THE NICE GUIDELINES
What it means for us

NAPS STUDY DAY ON WOMEN'S HEALTH 2017

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NICE Guide Lines

- Good points: -
  - ✦ That we are all here!

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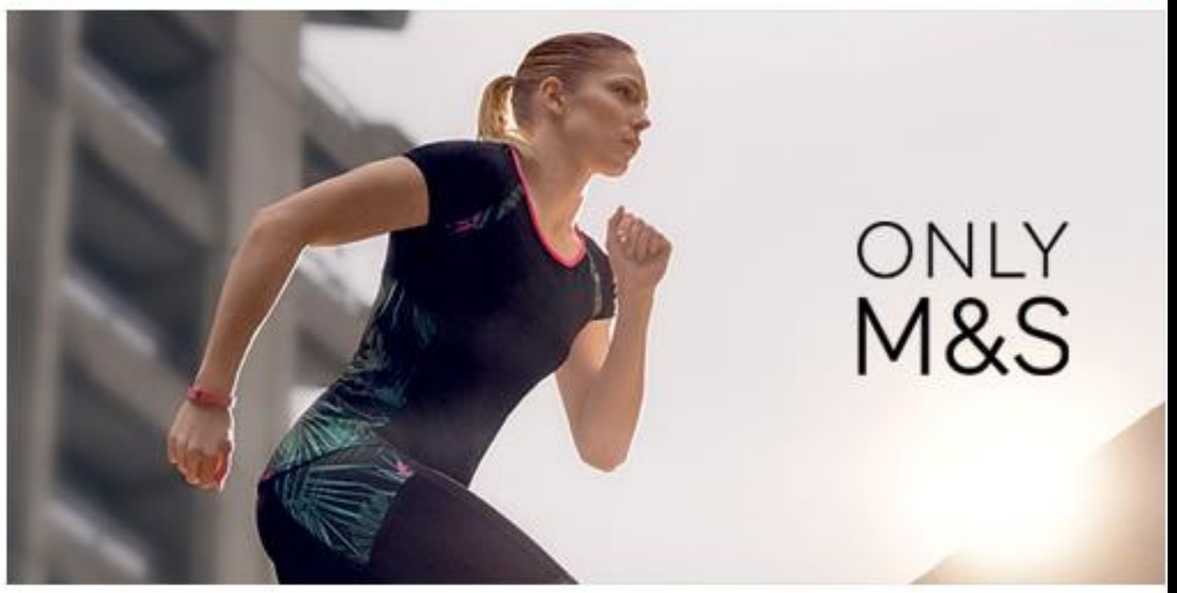

HRT: who can you believe?

by BEEZY MARSH, Daily Mail

Hundreds of thousands of British women may have abandoned HRT needlessly, it emerged yesterday.

More than half the 1.7million users in this country stopped taking it last year after research here linked the treatment to breast cancer.

But an American study yesterday contradicted those findings and said hormone replacement therapy may still be the best treatment for many menopausal women.

Experts condemned the confusion and said Government health officials had jumped the gun by warning women off HRT.

One said it effectively turns the clock back to the 1960s, when middle-aged women were expected to get through the "change of life" as best they could.

HRT works by replacing hormones lost at the time of the menopause. It can be taken as a pill, patch or a nasal spray.

Doctors were last year banned by the Government's Committee on Safety of Medicines from prescribing it as a treatment for the "brittle bone" disease osteoporosis and can give it to women only in the 'short term'.

Over the past two years, studies have raised fears that HRT is responsible for breast cancer, strokes and heart disease. One warned that the risks of taking it outweighed the benefits - sparking panic among the 1.7million British users. But U.S. research now ng evidence that oestrogen-only HRT does not cause an increase in

10 March 2015 Last updated at 20:14

HRT linked to clots - and possibly stroke - study finds

By Michelle Roberts
Health editor, BBC News online

Thrombosis can affect women over 50

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The Telegraph

Wednesday 11 March 2015

HRT could halve the risk of heart disease, Oxford University research suggests

A major study by Oxford University suggests that women who take HRT within a decade of the menopause have far lower death rates and half the risk of heart disease

8 38 2 7 48 Email

The benefits and risks of HRT to prevent symptoms of the menopause have been debated for years Photo: ALAMY (POSED BY

THE MENOPAUSE LEFT ME FLAT... I LOST MY MOJO

*She's just been through it – and here Lorraine Kelly tells **Jenny Johnston** how the experience floored her, what she did about it, and why it's ridiculous that discussing it is still taboo*

show. In it special guests will talk about their experiences and Lorraine will be grilled by Dr Hilary. 'The tables will be turned,' she laughs.

It's brave of her to open up about her own menopause though, and still quite unusual. 'It's ridiculous isn't it?' she scoffs. 'It's the last taboo! We still don't talk about it, even with our own girlfriends. I mean, it was madness that it didn't even occur to me that the menopause was to blame. I think it's changing. I know we had Carol Vorderman on the show a while back. She went through a terrible time, just terrible. I wasn't nearly as bad. But I think it did bring home to me how women need to talk about it, and not just sit at home wondering what's wrong with them, being depressed. It's natural! As a woman you get periods, you have your child-bearing years, and then you have the menopause. Some women find it ... Others feel sad that it's the end of a chapter of their lives. But it's the start of a new chapter too.

Whatever, I think it's something we need to talk about – men too. I ... discussing it with Steve and ... that he wonders if his own ... who's no longer with us, had ... a hard time of it because ...

... Kelly the job. This is a ... 's just been off clubbing ... By all accounts she put ... to shame by still being ... floor at 4am. Clear evi... has well and truly got ... Is she bothered about ... habits raising eyebrows ...? Is she heck! 'I think ... about getting older is ... don't give a hoot about what people think you should be doing. In my 20s I would have got all embarrassed about things, saying, "What if I make a fool of myself?" Now I think, "So what?"'

So much so that today she's prepared to go public with another ambition that a decade ago she might have kept under wraps. 'I quite fancy doing a bit of acting,' she reveals. 'I've been in a few TV things, but always playing myself. Now I fancy doing it for real. I'd want to play a baddie though.'

> 'Why do we see ageing as something we have to fight?'

She's certainly not one for staying within her comfort zone. She tells me that next year she'll be fronting a very different sort of programme to her morning chat show. Wedding Day Winners sees her change not just channels (this one is on the BBC), but timeslots, moving into the Saturday evening zone. The show will involve couples actually getting married on TV – with their whole families pitching up for games and challenges. The prize? A honeymoon, of course. It sounds a bit bonkers, but right up her street. 'When I heard about it I thought, "Why has this not been done before, because it's great fun?"'

If she's on devil-may-care form today perhaps it's understandable. Lorraine has spent much of the summer in the Far East (her daughter Rosie is now working for a charity in Singapore), and her travels to Vietnam and Cambodia gave her much to think about as she 'hurtles towards 60'. The East's attitude to ageing, she says, is something we need to embrace. 'Those are places where getting older is revered. We have a crazy thing going on in the West where that experience isn't appreciated and people feel they have to be young – or look young – to be valued. How nuts is that?'

Her latest bugbear is the language we use to describe getting older, and particularly in relation to women. 'What I hate is the way we describe the ageing process as a "battle", as if it's something we need to fight. Why? I'd love to see more acceptance about it. Let's face it, when we're in our 50s, 60s and 70s we aren't going to look the way we did at 18.'

This is rich coming from a woman who looks younger at 57 than she did at 27. To be fair, she giggles at the comparison. 'No, you're right. I think I do. A lot of it is to do with the hair, but also it's because I'm fitter now than I ever was in my 20s and 30s. I'm more confident too, by a long way. Also you learn to know what suits you, looks-wise.'

What was her most embarrassing fashion phase? She asks how long I have. 'Well, when I was at TV-am, way back, we got a lot more help style-wise, but when we moved to GMTV in the early 90s I had a whole time of cardigans, mostly ones that were too big for me. I would say from my sort of mid-30s to when I turned 50 was my worst period as far as style goes.' Isn't that supposed to be a woman's prime? 'Not for me! I genuinely feel I'm in my prime now. I'm healthier. I feel better.'

Is she better at her job than she was in her 20s too? That's an interesting question for any woman in the TV industry, where the unwritten rule is that you have to be the right side of 35 to succeed. 'Absolutely,' she says. 'So much of doing live telly comes with experience, and I've been doing this job for long enough that I

NICE Guide Lines

- Good points: -
  - ✦ That we are all here!
  - ✦ Emphasis on “individualised care” and counselling
  - ✦ Proper “information giving” to include: -
    - Physiology of the menopause
    - Symptoms
    - Lifestyle measures
    - HRT – types, risks & benefits
    - Long term health implications

NICE Guide Lines

- Good points: -

✦ A recognition that it is not all about sweats & flushes.

Consider: -

- Moods
- Vaginal atrophy
- Sex & function
- MSK Symptoms

MENOPAUSE SYMPTOM QUESTIONNAIRE

All answers are treated with the strictest confidence.

Name..... Date of Visit ..... On HRT? YES / NO

The scoring system runs from 0 – 3 depending on the severity of your symptoms.
Box No. 0 = Not troubled at all.
Box No. 1 = Mildly troubled.
Box No. 2 = Moderately troubled.
Box No. 3 = Severely troubled.

Please clearly indicate by placing an X against the appropriate box and please do answer all the questions. Thank you for your assistance; your answers will enable us to rapidly understand the severity of your problem and on subsequent visits, will help us to identify the degree of success of the treatment.

	QUESTIONS	ANSWERS			
		0	1	2	3
General Problems:	Daytime Sweats & Flushes				
	Night-time Sweats & Flushes				
	Unable to Sleep				
	Headaches				
	Tiredness7				
	Loss of Energy				
	General Aches & Pains				
	General Itchiness				
	Formication (feeling of something crawling over you)				
Emotional Problems:	Tearfulness				
	Depression				
	Feeling of Unworthiness				
	Irritability				
	Anger				
	Bitterness				
	Panic Attacks				
	+/- Palpitations				
	Aggression				
Bladder Problems:	Daytime Frequency				
	Urgency				
	Urge Incontinence (leakage if you do not get there in time)				
	Stress Incontinence (leakage if you cough,sneeze or laugh)				
	Night-Time Frequency				
	Bed Wetting				
Sexual Problems:	Vaginal Dryness / Soreness				
	Vaginal Itching				
	Soreness / pain with intercourse				
	Loss of Libido (sex drive)				
	Difficulty Achieving Orgasm				
Personality Problems:	Loss of Memory				
	Loss of Concentration				
	Inability to Cope				

NICE Guide Lines

- Good points: -

✦ A recognition that it is not all about sweats & flushes.
Consider: -

- Moods
- Vaginal atrophy
- Sex & function
- MSK Symptoms

✦ Diagnosis – not to use FSH in women > 45 years (except in special circumstances)

NICE Guide Lines

- Good points: -

✦ Not overreacting to BTB in the 1st 3 months of usage. Report irregular bleeding after 3 months.

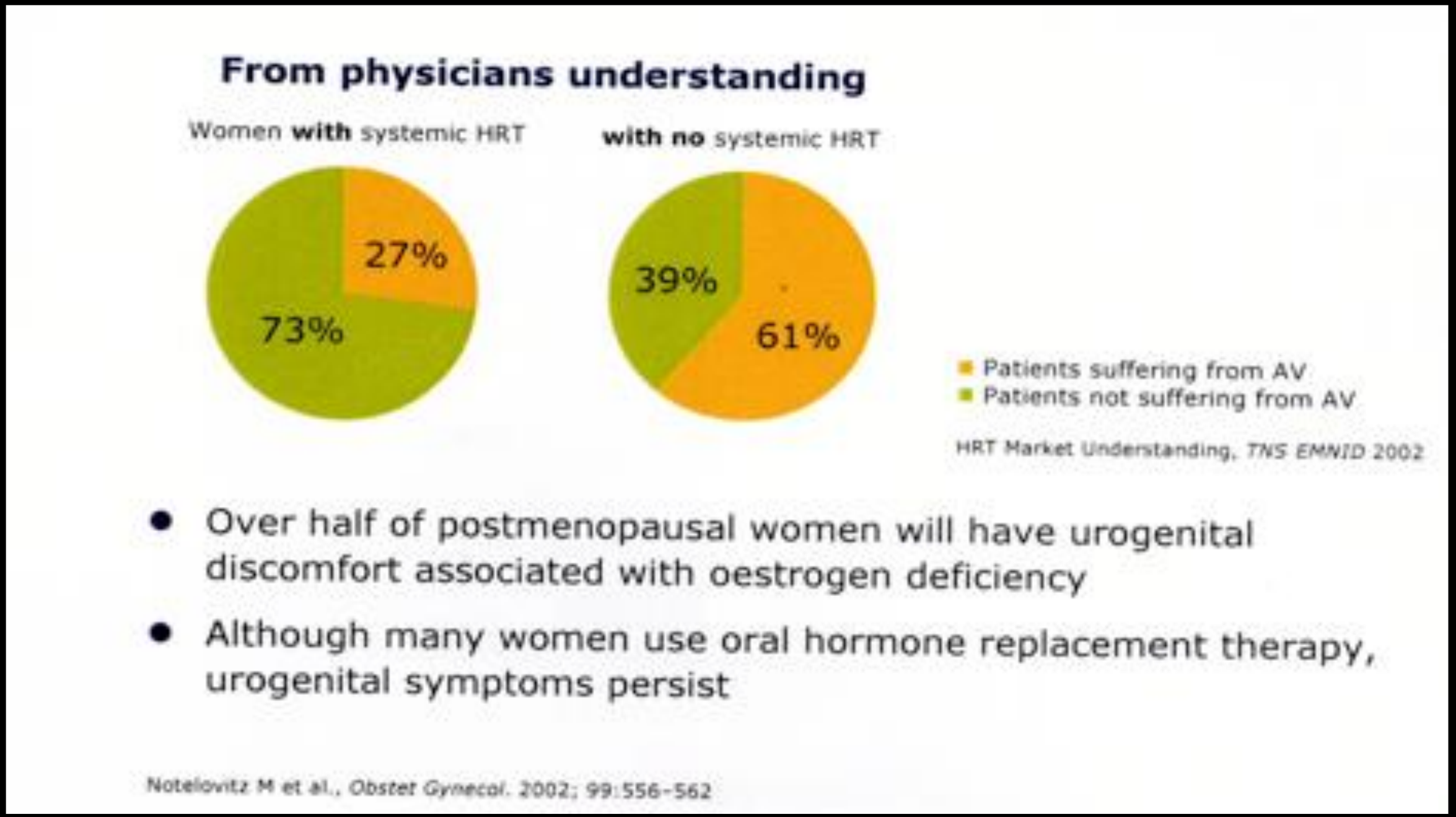
✦ NOT routinely using SSRIs, SNRIs and Clonidine for vasomotor symptoms or low moods if hormonally based. (Use for true depression.)

✦ HRT +/- CBT for low moods.

✦ Topical estrogens *for as long as it is needed* – often stopped after only three months.

✦ No need for ET estimations i.e. no hyperplasia.

✤ UROGENITAL ATROPHY



- Over half of postmenopausal women will have urogenital discomfort associated with oestrogen deficiency
- Although many women use oral hormone replacement therapy, urogenital symptoms persist

Notelovitz M et al., *Obstet Gynecol.* 2002; 99:556-562

TREATMENT OF VAGINAL ATROPHY 1

- Ovestin cream (estriol 0.1%)
- Gynest Cream (estriol 0.01%)
- Vagifem vaginal pessary (estradiol 10ug/applicator)
- Estring: Vaginal ring pessary (estradiol 7.5ug/24 hours) 3 monthly changes
- Estropipate Vaginal Cream HRT

Does not require progesterone opposition to protect endometrium as minimal amounts absorbed in systemic circulation

TREATMENT OF VAGINAL ATROPHY 2

- KY Jelly
- Replens
- Sylk
- Yes

- Vagi-soy

- Wild Yam Cream Menopause Naturals® All Natural Phyto-Estrogen Cream (Every ounce contains 150 mg of pomegranate juice extract, a natural source of estrone, and 100 mg of red clover extract)
- OxyPep Cream

Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition?

Climacteric. 2016 Apr;19(2):151-61. doi: 10.3109/13697137.2015.1124259. Epub 2015 Dec 26. Edwards D1, Panay N2.
Author information

Abstract

Vaginal dryness is a common condition that is particularly prevalent during and after the menopause, and is one of the symptoms of vulvovaginal atrophy/genitourinary syndrome of menopause. The impact of vaginal dryness on interpersonal relationships, quality of life, daily activities, and sexual function can be significant, but is frequently underestimated. Furthermore, barriers exist to treatment-seeking, and this condition is often underreported and undertreated. Greater education about vaginal dryness and the range of available treatments is essential to encourage more women to seek help for this condition. Personal lubricants and moisturizers are effective at relieving discomfort and pain during sexual intercourse for women with mild to moderate vaginal dryness, particularly those who have a genuine contraindication to estrogen, or who choose not to use estrogen. However, there is a distinction between lubricants and moisturizers, and notable differences between commercially available products. Women should be advised to choose a product that is optimally balanced in terms of both osmolality and pH, and is physiologically most similar to natural vaginal secretions. A series of recommendations for the use of vaginallubricants and moisturizers, either on their own or in combination with systemic or topical hormone replacement therapy, is presented.

KEYWORDS:

Cytotoxicity; genitourinary syndrome of menopause; lubricant; moisturizer; osmolality; vaginal dryness; vulvovaginal atrophy

NICE Guide Lines

- Good points: -

✦ Gradually reducing HRT when patient is coming off treatment – *reduces recurrence of symptoms.*

✦ Not associated with increased risk of diabetes.

✦ No adverse effect on blood sugar control.

✦ Big emphasis on NO risk of VTEs with patches.

VTE

- **Risk increases with:**

  estrogen dose

  age

  BMI

- **Greater during the 1st yr of use**

Canonico M, Plu-Bureau G, Lowe G, BMJ 2008, 336 DOI:10.1136/bmj.39555.441944 BE

- **Oral, but not transdermal, estrogens are associated with a higher risk of recurrent VTE**

  transdermal HR 1.0 (95% CI:0.4 -2.4)

  oral HR 6.4 (95% CI:1.5-27.3)

Olie V, Plu-Bureau G, Conrad J et al Menopause 2011 May(18) 5:488-93

STROKE

- **Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study.**
- DESIGN
  - Population based nested case-control study.
  - 400 GP practices in UK contributing to the GP Research Database.
  - Cohort of all women in the database aged 50-79 yrs, 01/1/87- 31/10/06
  - Each case of stroke matched to 4 controls
  - Exposure to HRT categorised into E_2, E+P, P only, Tibolone.
  - Estrogens were further subdivided according to the route of administration and dose
- RESULTS:
  - 15,710 cases of stroke matched to 59 958 controls.
  - The rate of stroke in the cohort was 2.85 per 1000 per year.
  - Adjusted rate ratio of stroke associated with current use of transdermal HRT was 0.95 (95% CI 0.75 - 1.20).
  - The risk of stroke was not increased with use of low oestrogen dose patches (rate ratio 0.81(0.62 to 1.05))
  - The risk was increased with high dose patches (rate ratio 1.89 (1.15 to 3.11)).
  - Current users of oral HRT had a higher rate of stroke than non-users (rate ratio 1.28 (1.15 to 1.42)) with both low dose and high dose.

Renoux C, Dell'aniello S, Garbe E, Suissa S. BMJ. 2010 Jun 3;340:c2519. doi: 10.1136/bmj.c2519.

NICE Guide Lines

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✦ Big emphasis on NO risk of VTEs with patches.

✦ NO increased risk of CVD if HRT prescribed < 60 years.

HRT and CARDIOVASCULAR PREVENTION 1

- Danish Study
- 1006 women, aged 45-58 yrs
- Recent post menopausal
- Randomised to receive HRT or placebo
- Women with an intact uterus were treated with triphasic E_2 + NET and women who had undergone hysterectomy received 2 mg E_2 a day.
- Intervention for 10 yrs – f/u for 16 yrs
- The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction.
- **(Schiebeck.LL, Rejnmark L, Tofteng CL et al. BMJ 2012; 345:e6409)**

HRT and CARDIOVASCULAR PREVENTION 2

- Results : -
- Women receiving Px early after the menopause have a significantly reduced risk of: -
  - Mortality (HR 0.57, 95% CI 0.30 to 1.08; P=0.084)
  - Heart Failure + MI + Death (HR 0.48, 95% CI 0.26 to 0.87; P=0.015)

Text

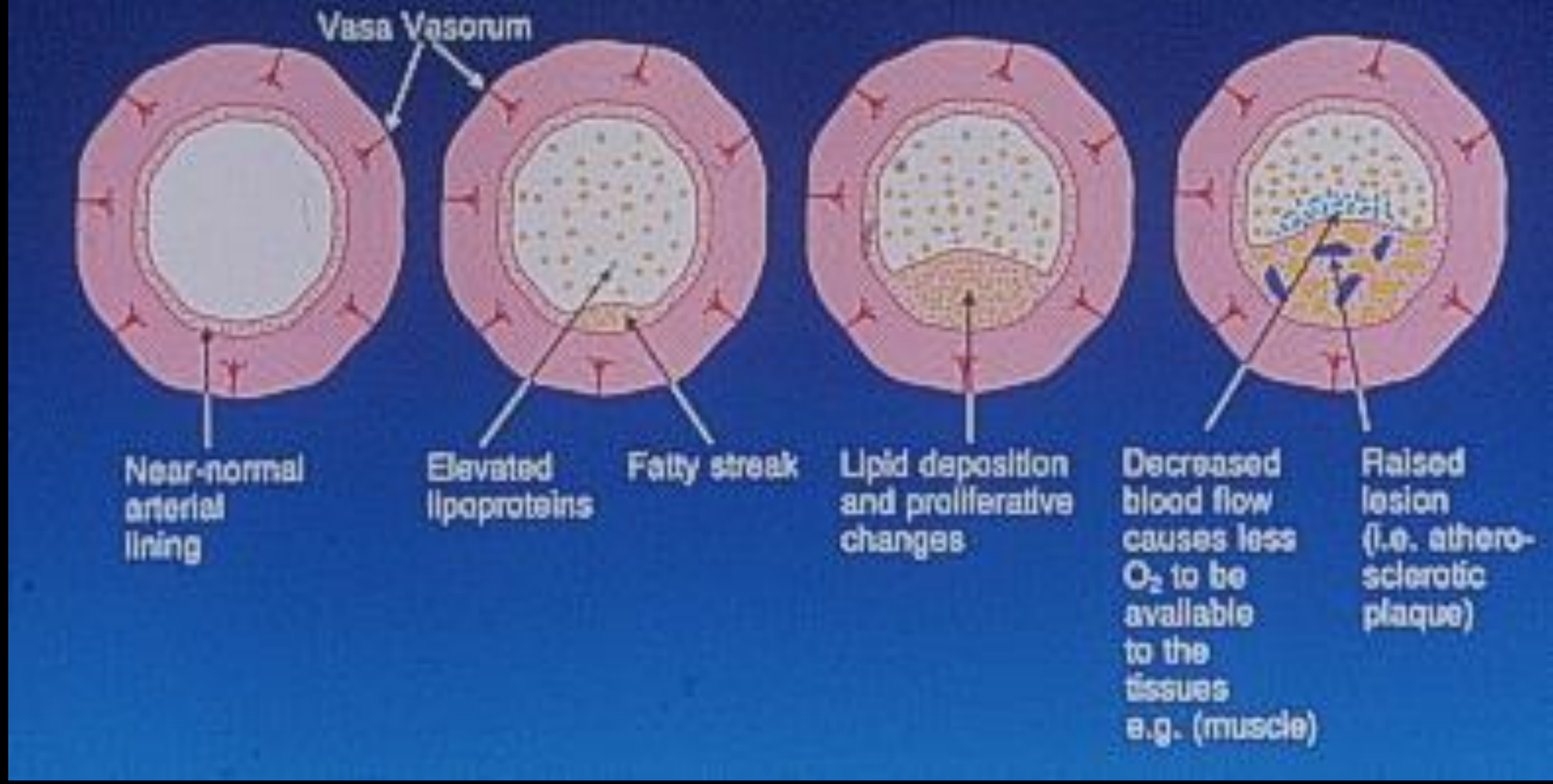
- No apparent increased risk of: -
  - Any cancer (HR 0.92, 95% CI 0.58 to 1.45; P=0.71)
  - Breast cancer (HR 0.58, 95% CI 0.27 to 1.27; P=0.17)
  - Stroke (HR 0.77 95% CI 0.35 to 1.70)
- DVT (HR 2.01 95% CI 0.18 to 22.16)

safety of long-term use

‘window of opportunity’

(Schiebeck.LL, Rejnmark L, Tofteng CL et al. BMJ 2012; 345:e6409)

STAGES OF ARTERIAL ATHEROSCLEROSIS



KEEPS 1: Kronos Early Estrogen Prevention Study

- 4 yrs double-blinded RCT
- Low dose oral or transdermal estrogen + cyclical progesterone
- 727 Healthy women 42-59 years (mean age : 52)
- Within 3 yrs of menopause
- Exclusion criteria!
  - Previous CVS
  - Levels of cholesterol or triglyceride necessitating Px
  - Obesity
  - Heavy smoking
- 3 arms :-
  - Premarin 0.45mg od + oral micronized progesterone 200mg 12 days
  - Estradiol 50µ patches + oral micronized progesterone 12 days
  - Placebo and oral placebo

KEEPS 2: Kronos Early Estrogen Prevention Study

- 466 women (64%) completed all 4 yrs of the trial
- 118 women (16%) discontinued study medication but continued f/u
- Both active arms had reduced climacteric symptoms cf placebo
- Both active arms had enhanced BMD cf placebo
- Both active arms had improved vaginal lubrication and reduced dyspareunia, on sexual function questionnaires, cf placebo
- t-E_2 gp had enhanced arousal and desire while the o-CEE did not

KEEPS 3: Kronos Early Estrogen Prevention Study

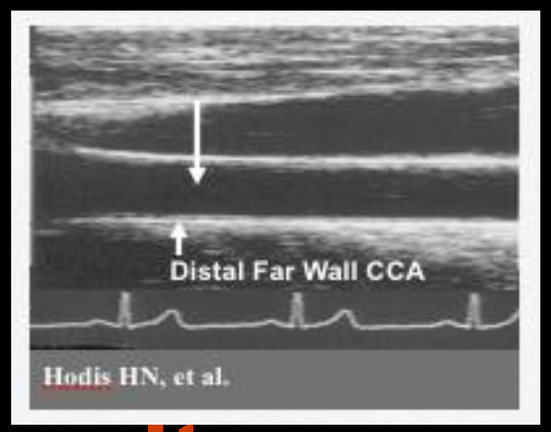
- o-CEE and t-E_2 showed no effect on systolic or diastolic BP
- o-CEE increased HDL – chol
- decreased LDL – chol
- increased triglyceride and CRP
- T-E_2 was neutral to lipid markers
- Improved glucose levels and insulin sensitivity
- No significant difference in rates of:
  - Ca Breast
  - Endometrial cancer
  - MI
  - TIA or stroke
  - VTE

} Between the 3 gps.

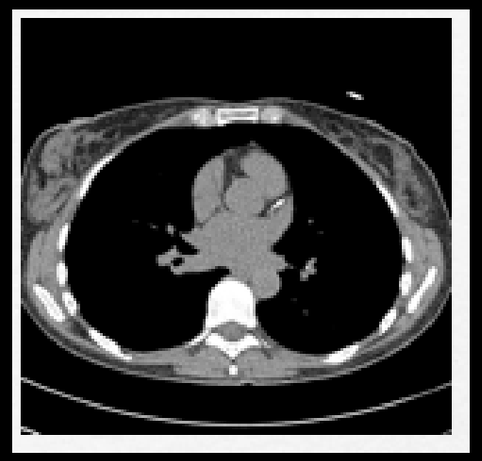
Confounder : young & generally healthy population so low incidence of events & small study size

Progression of atherosclerosis

Annual u/s imaging studies to estimate thickening of the walls of the Common Carotid As



Coronary artery calcium (CAC) also assessed via high-resolution CAT scans, pre- and post-study



- **Results**
- **Carotid A. U/S studies**
- **v.small changes**
- **similar rates of progress in all 3 gps**
- **Trend towards less progression of CAC in the HRT gps cf placebo (10.5% on o-CEE, 12.8% on t-E2, 14.3% on placebo)**
- **Increases occurred in women who already had some CAC changes at baseline!**
- **Increases in 5% of women with CAC of 0**
- **Increases in 67% of women with CAC>0 had increases of 5+ units**

ELITE trial

- 504 women, studied 2-5 yrs. <6yrs or >10 yrs postmenopausal
- Carotid artery vessel wall thickness
- RCT, HRT vs placebo
- HRT-1mg oral estradiol / vaginal progesterone
- Within 6 years of menopause
- 50% statistically significant reduction
- No benefit when HRT started >10 years post menopause

Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the Menopausal Hormone timing hypothesis. Hodis H et al Menopause 2015

Timing

- Majority of women over 60
- Under 60 per 1000 women over 7 years:

➢ 6 fewer deaths

➢ 8 fewer heart disease

➢ 5 extra blood clots

No change in previous conclusions, just more worried women!

In addition..

- Observational nationwide Study Finland
- 489,105 women using HRT, 1994 to 2009
- CHD death reduced by 18 to 54% in users
- Positively related to HRT exposure time
- Stroke death reduced by 18 to 39% in users
- Not clearly related to exposure time
- All cause mortality reduced by 12 to 38% in users
- All risk reduction comparable starting before, at or after age 60

Absolute terms

- Per 1000 women using any HRT for at least 10 years

➢ 19 fewer CHD deaths

➢ 7 fewer stroke deaths

Mikkola TS, Tuomikoski P, Lyytinen H et al. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. Menopause 2015 Mar 23. Epub ahead of print

NICE Guide Lines

- Good points: -

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✦ Not associated with increased risk of diabetes.

✦ No adverse effect on blood sugar control.

✦ Big emphasis on NO risk of VTEs with patches.

✦ NO increased risk of CVD if HRT prescribed < 60 years.

Table 1 Absolute rates of coronary heart disease for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in coronary heart disease incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 26.3 per 1000[1])			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on oestrogen alone	RCT estimate[2]	6 fewer (-10 to 1)	No available data	No available data	6 fewer (-9 to -2)
	Observational estimate[3]	6 fewer (-9 to -3)	No available data	No available data	No available data
Women on oestrogen + progestogen	RCT estimate[2]	5 more (-3 to 18)	No available data	No available data	4 more (-1 to 11)
	Observational estimate[3]	No available data	No available data	No available data	No available data

HRT, hormone replacement therapy; RCT, randomised controlled trial

For full source references, see Appendix M in the full guideline.

[1] Results from Weiner 2008 were used for the baseline population risk estimation.

[2] For women aged 50–59 years at entry to the RCT.

[3] Observational estimates are based on cohort studies with several thousand women.

Table 2 Absolute rates of stroke for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in stroke incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 11.3 per 1000[1])			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on oestrogen alone	RCT estimate[2]	0 (-5 to 10)	No available data	No available data	1 more (-4 to 9)
	Observational estimate[3]	3 more (-1 to 8)	No available data	No available data	No available data
Women on oestrogen + progestogen	RCT estimate[2]	6 more (-2 to 21)	No available data	No available data	4 more (-1 to 13)
	Observational estimate[3]	4 more (1 to 7)	No available data	No available data	No available data

HRT, hormone replacement therapy; RCT, randomised controlled trial

For full source references, see Appendix M in the full guideline.

[1] Results from Weiner 2008 were used for the baseline population risk estimation.

[2] For women aged 50–59 years at entry to the RCT.

[3] Observational estimates are based on cohort studies with several thousand women.

NICE Guide Lines

- Good points: -

✦ Use of absolute values to describe risk NOT percentages.

✦ Clear risk-benefit messages and tables for use when counselling patients.

✦ Benefits of HRT on osteoporosis.

✦ Benefits last longer after cessation of medication (“hangover effect”) if HRT is taken for longer.

Table 4 Absolute rates of any fragility fracture for HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in any fragility fracture incidence per 1000 menopausal women (95% confidence interval) (see footnotes for information on baseline population risk and length of follow-up time over which absolute risk difference is calculated)			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on any HRT	RCT estimate[1]	23 fewer (-10 to -33)[3]	25 fewer (-9 to -37)[4]	No available data	No available data
	Observational estimate[2]	16 fewer (-15 to -18)[5]	15 fewer (-11 to -17)[5]	18 fewer (-15 to -20)[5]	2 more (-19 to 27)[6]

HRT, hormone replacement therapy; RCT, randomised controlled trial

For full source references, see Appendix M in the full guideline.

Absolute risks calculated by using the baseline population risk in the control arm for each analysis, following GRADE methodology.

[1] For women aged 50–59 years at entry to the RCT.

[2] Observational estimate is based on cohort studies with several thousand women.

[3] Baseline population risk = 69 per 1000 women (follow-up: 3.43 years).

[4] Baseline population risk = 78 per 1000 women (follow-up: 3.71 years).

[5] Baseline population risk = 15.4 per 1000 women (follow-up: 2.8 years).

[6] Baseline population risk = 106 per 1000 women (follow-up: 5 years).

NICE Guide Lines

- Good points: -

✦ Use of absolute values to describe risk NOT percentages.

✦ Clear risk-benefit messages and tables for use when counselling patients.

✦ Benefits of HRT on osteoporosis.

✦ Benefits last longer after cessation of medication (“hangover effect”) if HRT is taken for longer.

✦ “Offer all women with, or at high risk of breast cancer information on ALL treatment options”.

Table 3 Absolute rates of breast cancer for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

		Difference in breast cancer incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 22.48 per 1000[1])			
		Current HRT users	Treatment duration <5 years	Treatment duration 5–10 years	>5 years since stopping treatment
Women on oestrogen alone	RCT estimate[2]	4 fewer (-11 to 8)	No available data	No available data	5 fewer (-11 to 2)
	Observational estimate[3]	6 more (1 to 12)[4]	4 more (1 to 9)	5 more (-1 to 14)	5 fewer (-9 to -1)
Women on oestrogen + progestogen	RCT estimate[2]	5 more (-4 to 36)	No available data	No available data	8 more (1 to 17)
	Observational estimate[3]	17 more (14 to 20)	12 more (6 to 19)	21 more (9 to 37)	9 fewer (-16 to 13)[5]

HRT, hormone replacement therapy; RCT, randomised controlled trial

For full source references, see Appendix M in the full guideline.

[1] Office for National Statistics (2010) breast cancer incidence statistics.

[2] For women aged 50–59 years at entry to the RCT.

[3] Observational estimates are based on cohort studies with several thousand women.

[4] Evidence on observational estimate demonstrated very serious heterogeneity without plausible explanation by subgroup analysis.

[5] Evidence on observational estimate demonstrated very serious imprecision in the estimate of effect.

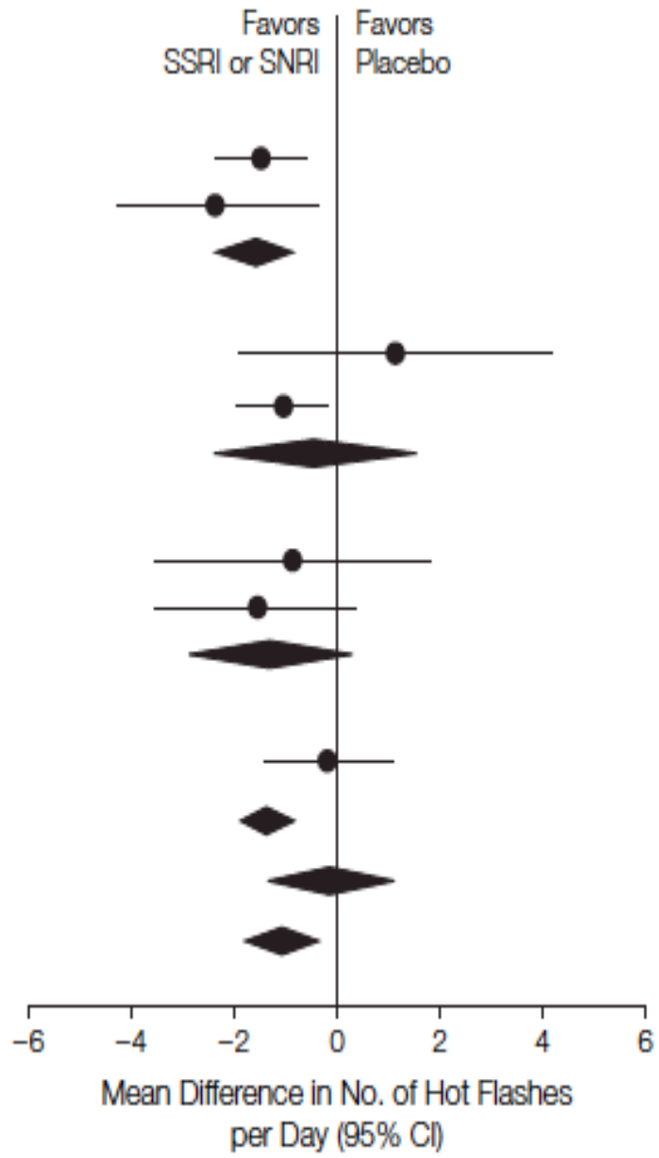
CLONDINE: EVIDENCE BASE

HOT FLUSH REDUCTION	NO HOT FLUSH REDUCTION
Pandya KJ.,Raubertus R.F, Flynn H.E et al. Ann Intern. Med 2000; 132(10)788-93 ✪ (194 women, Ca Breast pts, 8 week duration, 4 weeks F/U) Edington et al 1980 ⌫ (93 women, 4 weeks crossover) Nayomani et al, 1987 ⌫ (30 women, 8 weeks) subjective improvement only Nappi et al, 1991 ⌫ (36 women, 4 weeks) Goldberg et al, 1994 ✪ (116 women, 4 weeks crossover)	**Wren B G, Brown LB. Med. J.Aus 1986: 144: 369-70 ⌫ (crossover study – only 19 patients, 4 weeks)** **Bolli & Simpson, 1975 ⌫ (12 women, 2 weeks crossover) Clayden et al 1974 ✪ (100 women, 4 weeks crossover) Lindsay and Hart 1978 ⌫ (100 women, 6 weeks crossover)** **Salmi and Punnonen, 1979 ⌫ (40 women, 6 weeks crossover)**

Key: ✪ Fair study ⌫ Poor study

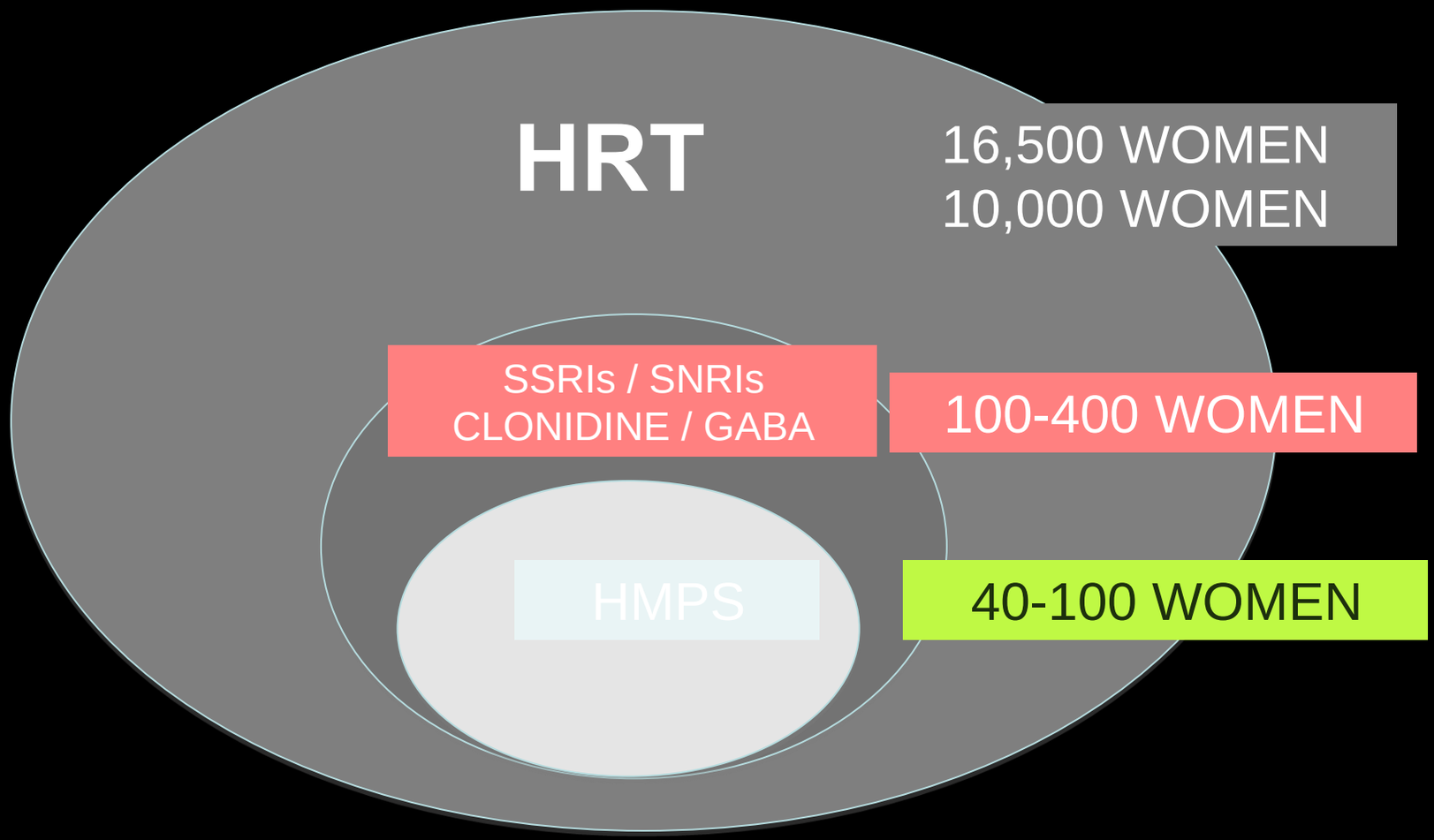
TRIALS OF SELECTED SEROTONIN RE-UPTAKE INHIBITORS (SSRIs) OR SEROTONIN REUPTAKE INHIBITORS (SNRIs)

Source	Dose	No. of Participants	Duration of Trial	Quality	Mean Difference (95% CI)
Paroxetine Trials					
Stearns et al,[29] 2003	12.5 or 25 mg/d*	165	6 wk	Good	−1.52 (−2.36 to −0.69)
Stearns et al,[30] 2005	10 or 20 mg/d	151	4 wk	Fair	−2.43 (−4.43 to −0.42)
Combined					−1.66 (−2.43 to −0.89)
Venlafaxine Trials					
Evans et al,[22] 2005	75 mg/d*	80	12 wk	Fair	1.10 (−1.94 to 4.14)
Loprinzi et al,[31] 2000	37.5 or 75 mg/d*†	167	4 wk	Good	−1.09 (−1.99 to −0.18)
Combined					−0.49 (−2.40 to 1.41)
Fluoxetine Trials					
Loprinzi et al,[32] 2002	20 mg/d	81	4 wk	Fair	−0.90 (−3.78 to 1.98)
Suvanto-Luukkonen et al,[23] 2005	20 mg/d‡	100	3 mo	Fair	−1.60 (−3.63 to 0.43)
Combined					−1.37 (−3.03 to 0.29)
Citalopram Trials					
Suvanto-Luukkonen et al,[23] 2005	20 mg/d‡	100	3 mo	Fair	−0.20 (−1.45 to 1.05)
Trials With SERM Use Combined§					−1.40 (−1.97 to −0.82)
Trials Without SERM Use Combined‖					−0.17 (−1.41 to 1.07)
All Trials Combined					−1.13 (−1.70 to −0.57)



Nelson HD(1), Vesco KK, Haney E, et al Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. 2066 JAMA, May 3, 2006—Vol 295, No. 17

COMPARISONS OF SCALE



NICE Guide Lines

- Good points: -

✦ Use of absolute values to describe risk NOT percentages.

✦ Clear risk-benefit messages and tables for use when counselling patients.

✦ Benefits of HRT on osteoporosis.

✦ Benefits last longer after cessation of medication (“hangover effect”) if HRT is taken for longer.

✦ “Offer all women with, or at high risk of breast cancer information on ALL treatment options”.

✦ Whole section on POI / POF

NICE Guide Lines

- Good points: -

✦ Pushing a change in delivery – challenging CCGs, Private Managers etc.

✦ Raising awareness of “Specialists” and Specialist Clinics.

✦ Suggesting Practice Nurses can attend the FSRH Special Skills Courses.

✦ Re-invigorating the role of the GPwSI.

✦ Menopause Clinics MUST be multi-disciplinary and jointly led by Nurse Consultant and a Consultant.

✦ Pushing new education programmes for public and professionals.

NICE Guide Lines

- Bad Points

✦ Naivety: -

- Will service provision be provided?
- Mismatch in vision vs reality
- Standard recommendations for R & D e.g. VTE, Breast Cancer and Progestogens etc. - but 47th RCOG Study Group recommended similar in 2004

NICE Guide Lines

- Bad Points

✦ Ambiguity in places: -

- “Some evidence that Isoflavones & Black Cohosh relieve vasomotor symptoms.”

COCHRANE DATABASE FOR HMPs

A total of 43 randomised controlled trials (4,364 participants) were included in this review.
Few were suitable for inclusion
Among the 5 RCTs taking Promensil – no satisfied preference with placebo
Strong placebo affect in most trials
Weak evidence for dietary Soya & Soya Extracts
Four trials that were not combined in meta-analyses showed benefit of high (> 30 mg/d) levels of genistein concentration.

Lethaby A1, Marjoribanks J, Kronenberg F,et al Phytoestrogens for menopausal vasomotor symptoms. Cochrane Database Syst Rev. 2013 Dec 10;12:CD001395. doi: 10.1002/14651858.CD001395.pub4.

Sixteen randomised controlled trials, recruiting a total of 2027 perimenopausal or postmenopausal womenAll studies used oral mono-preparations of black cohosh at a median daily dose of 40 mg, for a mean duration of 23 weeks.currently insufficient evidence to support the use of black cohoshthere is adequate justification for conducting further studies

Leach MJ1, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012 Sep 12;9:CD007244. doi:

NICE Guide Lines

- Bad Points

✦ Ambiguity in places: -

- “Some evidence that Isoflavones & Black Cohosh relieve vasomotor symptoms.”
- Information that “Tamoxifen should not be given with SSRIs, Paroxetine & Fluoxetine”, implies that they can be offered to some Breast Cancer patients.
- St John’s Wort – purity of preparation, efficacy, long term effects and risk of drug interactions all queried & highlighted – yet recommended for Breast Cancer patients!

Cautions with HMPs 1

- Use herbal remedies with caution in women with a contra-indication to oestrogen because some preparations have oestrogenic properties.
- St John's Wort interacts with other medications :

- it decreases the blood concentrations of cyclosporin, midazolam, tacrolimus, mitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline

➔ Cases have been reported where decreased cyclosporin concentrations have led to organ rejection.

- Possible BTB and contraceptive failure when used with COC

- Reduced efficacy with anti-epileptics

- It has been reported to induce serotonin syndrome when used in combination with SSRIs such as sertraline and paroxetine.

- Dong Quai, Gingseng - Bleeding when combined with Warfarin or aspirin (phenelzine and alcohol interact with Gingseng.)

CAUTIONS WITH HMPS 2

Beware of side effects of herbal remedies.

- Black Cohosh in high doses may cause vomiting, headaches, dizziness, low blood pressure, and limb pain

There have been more serious adverse events reported, including hepatotoxicity,

one case requiring liver transplantation.

- reactions.
- Ginkgo Biloba may produce mild gastrointestinal complaints and, rarely, allergic skin
- Ginseng in large doses may cause sleeplessness, oedema, and hypertonia

NICE Guide Lines

- Bad Points

✦ Ambiguity in places: -

- “Some evidence that Isoflavones & Black Cohosh relieve vasomotor symptoms.”
- Information that “Tamoxifen should not be given with SSRIs, Paroxetine & Fluoxetine”, implies that they can be offered to some Breast Cancer patients.
- St John’s Wort – purity of preparation, efficacy, long term effects and risk of drug interactions all queried & highlighted – yet recommended for Breast Cancer patients!
- Bazedoxifene/CEE compound – largely ignored.
- Testosterone

NICE Guide Lines

- Bad Points

✦ Follow up at three months – must be after 3 completed cycles. Stress review ‘as necessary’, or pt. not seen again for one year.

✦ Vagifem usage – “appropriate dose” - danger only 10µg Often needs to use 2x10µg pessaries i.e. 20µg initially, if really sore.

✦ Tables are good – but a little indigestible.

NICE Guide Lines

- Bad Points
  - ✦ Loopholes, not really covered:
  - The late 40's perimenopausal patient
  - Women in their 50's who are asymptomatic, but have osteopenia/osteoporosis
  - Testosterone usage – use after re-estrogenisation, but not really covering implementation. (See ESHRE & International Endocrine Guidelines)

NICE Guide Lines

- NICE Evaluation Methods

✦ NICE are not the same as Cochrane Database Syst. Rev.

- They do eject poor quality papers
- Also good papers if no economic evaluation
- All papers sponsored by Pharma (even if good quality).

✦ The model for economic evaluation uses a Network Meta-Analysis (NMA) based on a clear model & set pathways. Anything outside the model is not truly covered.

- Model for a standard healthy woman in 50s