Personalizing the road ahead for women experiencing vasomotor symptoms during menopause

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME activities*
- *touchIME accepts no responsibility for errors or omissions*

Expert faculty

Mr Nicholas Panay

Consultant Gynaecologist and Honorary Senior Clinical Lecturer, Imperial College Healthcare NHS Trust and Chelsea & Westminster Hospital NHS Foundation Trust, London, UK

Prof. Dr. med. Petra Stute

Deputy Director, Department of Gynecologic Endocrinology and Reproductive Medicine, University Hospital of Bern, Bern, Switzerland

Dr Marla Shapiro

CCFP, MHSc, FRCPC, FCFP, NCMP Professor, Department of Family and Community Medicine, University of Toronto, Toronto, Canada

touch ENDOCRINOLOGY®

Agenda

Welcome and Introduction
Mr Nicholas Panay

Beyond the confusion: What are the current evidence-based MHT recommendations for treating menopause?
Dr Marla Shapiro

Beyond MHT: What non-hormonal alternatives are available for treating vasomotor symptoms in women going through menopause?
Prof. Dr. med. Petra Stute

Beyond a one-size-fits-all approach: How can we make personalized care a reality for women going through menopause?
A case-based discussion
All faculty

MHT, menopausal hormone therapy.

touch ENDOCRINOLOGY®

Learning objectives

- Describe the most up-to-date, evidence-based recommendations for MHT, including factors to consider when determining whether MHT is the most appropriate treatment option for different patient groups
- Discuss alternatives to MHT, including non-hormonal treatment pathways on the horizon
- Translate evidence-based knowledge into the personalized treatment of vasomotor symptoms in women going through menopause

MHT, menopausal hormone therapy.

Common menopause symptoms

- Menopause is associated with multiple symptoms that can negatively impact women's QoL
- Common menopause symptoms include:[1–3]

Hot flushes/night sweats (vasomotor symptoms)

Vaginal dryness and dyspareunia

Sleep disturbance and insomnia

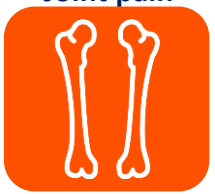
Low mood and depression

Reduced libido

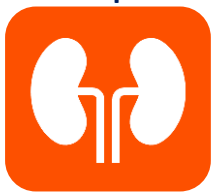
Poor cognitive function

Low energy levels

Joint pain



Urinary frequency and pain



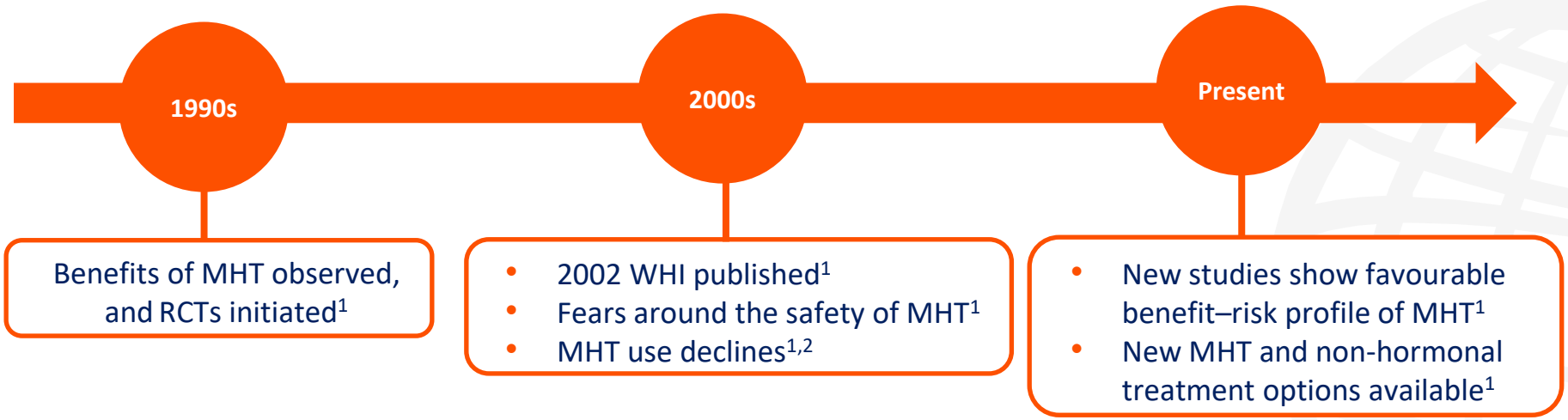
Headaches

QoL, quality of life.

1. Santoro N, et al. *Endocrinol Metab Clin North Am.* 2015;44:497–515; 2. Peacock K, Ketvertis KM. Menopause 2020 Treasure Island (FL): StatPearls Publishing; 3. NHS. Menopause Symptoms. August 2018. Available at: www.nhs.uk/conditions/menopause/symptoms/ (accessed 5 February 2021).

touch ENDOCRINOLOGY®

MHT: A history



Symposium focus: efficacy and safety of hormonal and non-hormonal therapies, and personalization of treatment

MHT, menopausal hormone therapy; RCT, randomized controlled trial; WHI, Women's Health Initiative.

1. Cagnacci A, Venier M. *Medicina.* 2019;55:602; 2. Crawford S, et al. *Menopause.* 2018;26:588–97.

Impact of MHT on menopause symptoms

- There is now evidence demonstrating that, in certain patient groups, MHT can:[1,2]


Reduce vasomotor symptom frequency by up to 75%


Reduce bone loss and fracture risk


Positively impact coronary heart disease risk


Help alleviate sleeping disorders


Improve mood and menopause-associated depression

MHT, menopausal hormone therapy.

1. Fait F. *Drugs Context.* 2019;8:212551. 2. Rees M, et al. *Menopause Int*. 2008;14:40-5.

touch ENDOCRINOLOGY®

Menopause treatment: Where are we now?

- New therapies for managing menopause symptoms and risks are available or undergoing clinical trials:[1–5]

Hormonal therapies

- Estrogens and progestogens
- Selective tissue estrogenic activity regulator
- Tissue-selective estrogen complex
- Bio-identical compounded hormones*

Non-hormonal therapies

- Alpha-adrenergic antihypertensive
- SSRIs/SNRIs
- Perphines
- Complementary/ alternative medicines
- Anticonvulsants
- Anticholinergic agent
- KNDy agents
- Lifestyle modifications

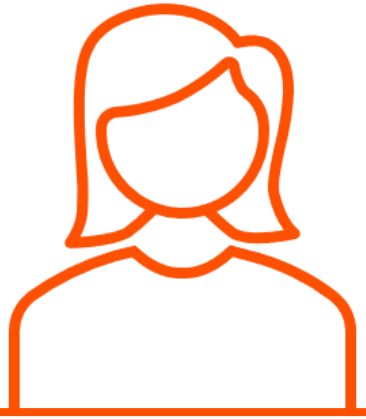
*Custom-compounded hormones that may include bio-identical hormones are not approved and have no data to substantiate claimed benefits over standard therapy.
KNDy, kisspeptin-neurokinin B-dynorphin system; SNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

1. Fait F. *Drugs Context.* 2019;8:212551; 2. Biglia N, et al. *Ecancermedicalscience.* 2019;13:909; 3. Trower M, et al. *Menopause*. 2020;27:498–505.
4. Pherin Pharmaceuticals. Available at: www.pherin.com/hormone-replacement-therapy.html (accessed 5 February 2021).
5. Sood R, et al. *J Am Board Fam Med.* 2011;24:202–10.

touch ENDOCRINOLOGY®

Moving towards a personalized approach

- Menopausal symptom treatment should be individualized and account for side effects, cautions and contraindications, including:



- **Age of menopause onset[1]**
- **Timing of treatment initiation[1]**
- **Family history[2]**
- **Risk of VTE[2]**
- **Risk of CHD[2]**
- **History/high risk of breast cancer[2]**

CHD, coronary heart disease; VTE, venous thromboembolism.

1. The North American Menopause Society. *Menopause.* 2017;24:728–53; 2. NICE guideline 23. 12 November 2015; updated December 2019. Available at: www.nice.org.uk/guidance/ng23/ (accessed 5 February 2021).

Clinical challenges associated with treatment

- Changes to recommendations and approval of new therapies have made it difficult to keep up-to-date with optimal management approaches

Cases submitted for discussion include women with:

1. A history of breast cancer
2. An increased CV risk
3. A history of endometriosis
4. Early menopause

CV, cardiovascular.

Continuing care through the COVID-19 pandemic

- Advise women about menopause issues using telephone or virtual consultations where possible[1]
- Telephone or virtual consultations are ideal for women with easy access to repeat menopause treatment prescriptions, particularly those who have been on treatment and have not been experiencing problems with their intake[1]
- Refer women to published tools and resources (these may be country-specific) to support menopause management with virtual and telephone consultations[2]

COVID-19, coronavirus disease 2019.

1. Hamoda H, et al. FSRH, RCOG, RCGP and BMS statement. 27 March 2020. Available at: www.fsrh.org/news/fsrh-rcog-rcgp-and-bms-statement-access-to-hormone-replacement/ (accessed 5 February 2021); 2. British Menopause Society. Primary Care Women's Health Forum. Primary Care Guide. March 2020. Available at: https://pcwhf.co.uk/wp-content/uploads/2020/05/PCWHF-Menopause-Management-remote-consultation-tool_V4.pdf (accessed 5 February 2021).

Agenda

Welcome and Introduction
Mr Nicholas Panay

Beyond the confusion: What are the current evidence-based MHT recommendations for treating menopause?
Dr Marla Shapiro

Beyond MHT: What non-hormonal alternatives are available for treating vasomotor symptoms in women going through menopause?
Prof. Dr. med. Petra Stute

Beyond a one-size-fits-all approach: How can we make personalized care a reality for women going through menopause?
A case-based discussion
All faculty

MHT, menopausal hormone therapy.

touch ENDOCRINOLOGY®

Beyond the confusion: What are the current evidence-based MHT recommendations for treating menopause?

Dr Marla Shapiro C.M.

CCFP, MHSc, FRCPC, FCFP, NCMP
Professor,
Department of Family and Community Medicine,
University of Toronto,
Toronto, Canada

touch ENDOCRINOLOGY®

Menopausal hormone therapy

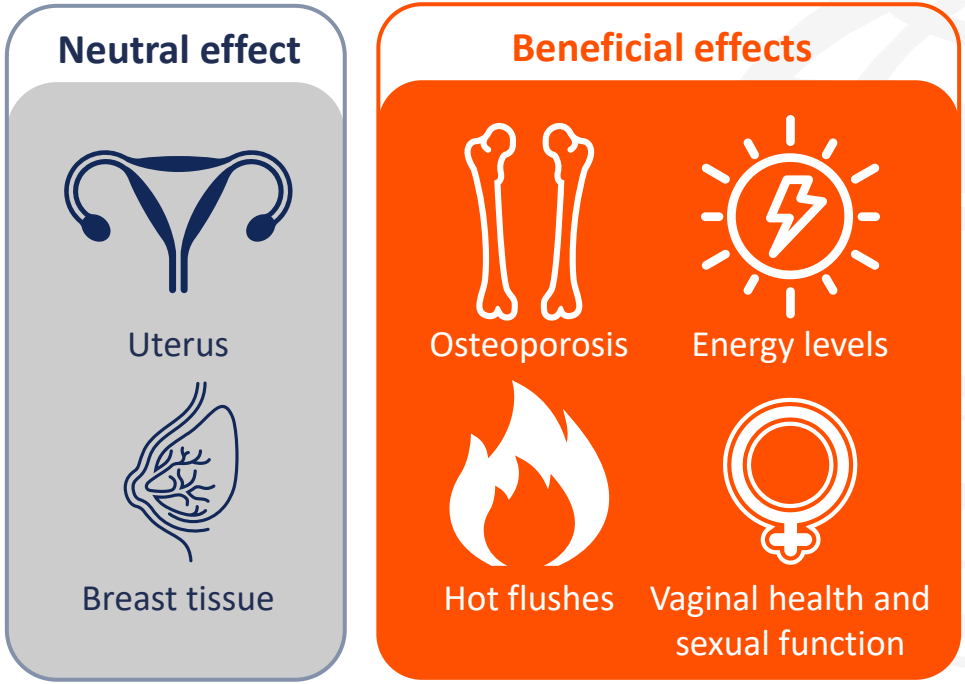
- Safe and effective option for menopausal vasomotor and genitourinary symptoms, and prevention of bone loss in healthy, younger postmenopausal women
  - Vasomotor symptoms especially important
- Estrogen therapy (plus a progestogen if uterus intact) is the gold standard of therapy for menopausal symptoms
  - A TSEC, comprising a fixed combination of CEE and bazedoxifene, can be used for the same indication
  - The STEAR tibolone is another alternative in certain cases
  - All administration routes are equally effective
  - Both synthetic and animal estrogens (CEE) are available

CEE, conjugated equine estrogens; MHT, menopausal hormone therapy; STEAR, selective tissue estrogenic activity regulator; TSEC, tissue-selective estrogen complex.

Fait T. *Drugs Context*. 2019;8:212551.

TSEC: Tissue-selective estrogen complex

- Combination of CEE with a SERM instead of a progestogen[1]
- Bazedoxifene is a SERM with estrogen antagonist effects on endometrial and breast tissue, and agonist effects on bone[1]
- CEE + bazedoxifene is the first TSEC approved by the FDA and EMA[2]

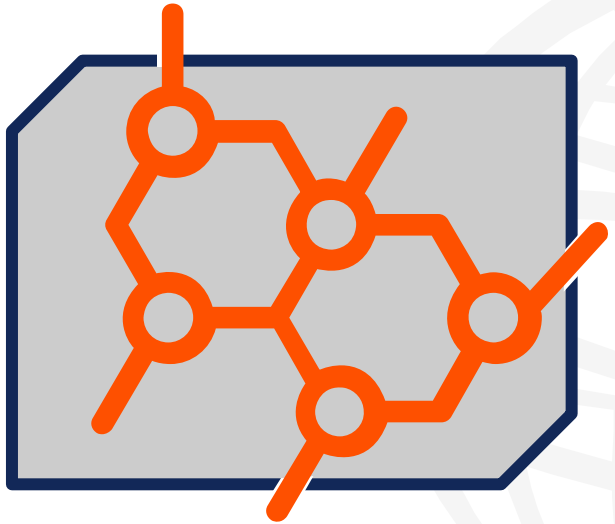


CEE, conjugated equine estrogens; EMA, European Medicines Agency; FDA, US Food and Drug Administration; SERM; selective estrogen receptor modulator; TSEC, tissue-selective estrogen complex.

1. Lello S, et al. *Int J Endocrinol*. 2017;2017:5064725; 2. Baquedano L, et al. *Reprod Med Int*. 2018;1:004.

Bio-identical hormones for MHT

- Identical chemical and molecular structure to endogenous human hormones
- Estradiol (E2) and progesterone are commercially approved
- Bio-identical *compounded* hormone therapies are custom-compounded hormones that may include bio-identical hormones, but are *not* approved and have no data to substantiate claimed benefits over standard therapy

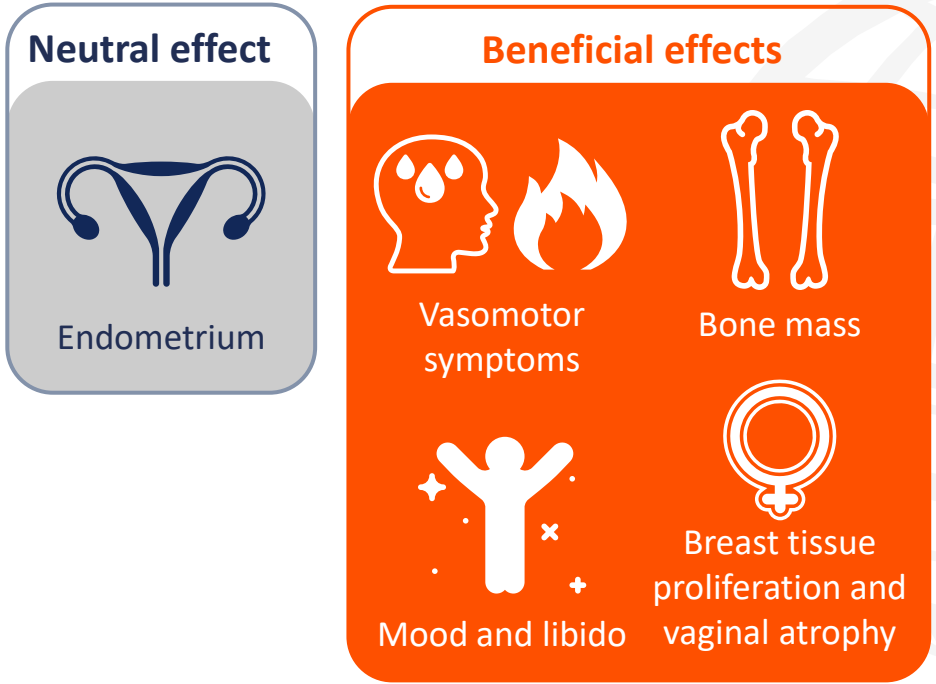


MHT, menopausal hormone therapy.

Sood R, et al. *J Am Board Fam Med.* 2011;24:202–10.

STEAR: Selective tissue estrogenic activity regulator

- Tibolone is a progestogen with tissue-selective weak estrogenic, progestogenic and androgenic activity[1]
- Improved menopausal symptoms within 6 months of use[2]
- Treatment of choice for women with endometriosis history or unwanted side effects with conventional MHT[1]



MHT, menopausal hormone therapy.

1. Fait T. *Drugs Context*. 2019;8:212551; 2. Kim HK, et al. *J Menopausal Med.* 2019;25:123–9.

Women's Health Initiative MHT trials

27,347 postmenopausal women (50–79 years old)[1,2]

Estrogen plus progestin component[1]	Estrogen alone component[2]
16,608 women with an intact uterus	10,739 women with prior hysterectomy
CEE 0.625 mg/d + MPA 2.5 mg/d (n=8,506) or placebo (n=8,102)	CEE 0.625 mg/d (n=5,310) or placebo (n=5,429)
Ended: May 2002	Ended: February 2004

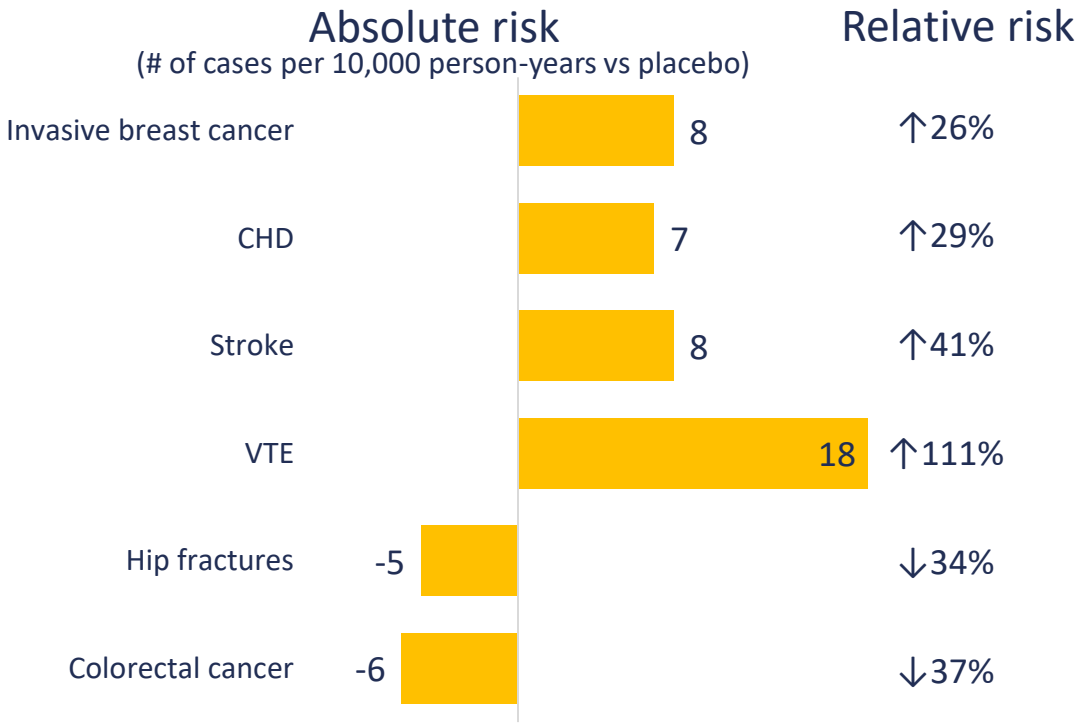
Efficacy endpoint: CHD incidence[1,2]
Safety endpoint: invasive breast cancer incidence[1,2]

CEE, conjugated equine estrogens; CHD, coronary heart disease; d, day; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.

1. Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321–33; 2. Women's Health Initiative Steering Committee. *JAMA*. 2004;291:1701–12.

touch ENDOCRINOLOGY®

WHI combination EPT trial: Initial overall results



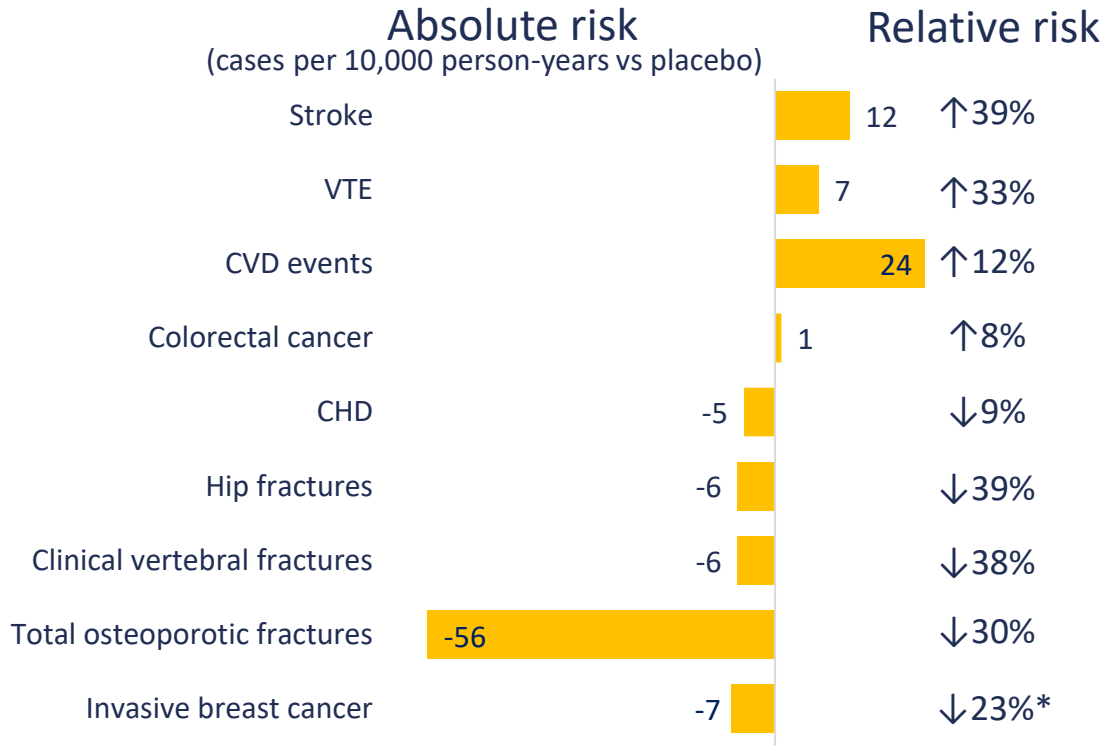
Overall initial conclusions after a mean follow-up of 5.2 years:

- Unfavourable risk/benefit profile
- CEE/MPA should not be initiated or continued for primary prevention of coronary heart disease

CEE, conjugated equine estrogens; CHD, coronary heart disease; EPT, estrogen-progestogen therapy; MPA, medroxyprogesterone acetate; VTE, venous thromboembolism; WHI, Women's Health Initiative.

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321–33.

WHI monotherapy ET trial: Initial overall results



Overall initial conclusions at mean follow-up of 6.8 years:

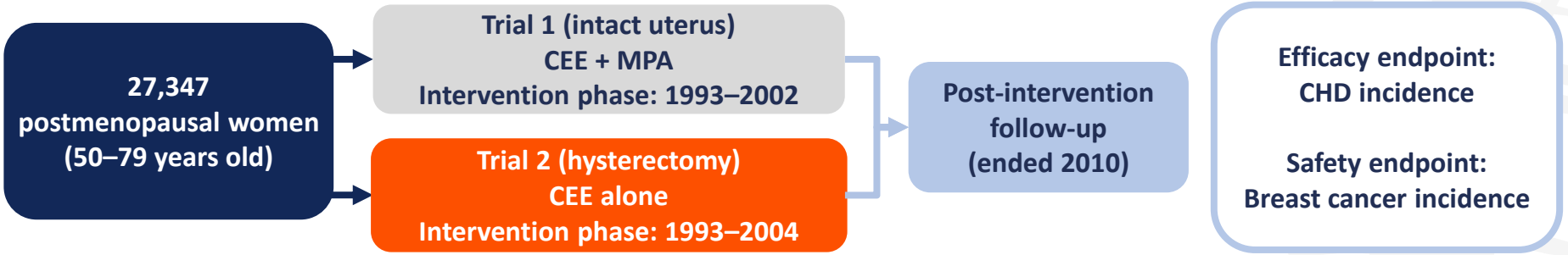
- No overall benefit
- CEE should not be recommended for chronic disease prevention in postmenopausal women

*p=0.06

CEE, conjugated equine estrogens; CHD, coronary heart disease; CVD, cardiovascular disease; ET, estrogen therapy; VTE, venous thromboembolism; WHI, Women's Health Initiative.

Women's Health Initiative Steering Committee. *JAMA*. 2004;291:1701–12.

Women's Health Initiative MHT trials: Extended post-intervention follow-up



- Vasomotor symptoms (hot flushes and night sweats) included as stratification factors and self-reported endpoints
- <2% (intact uterus) and <4% (hysterectomy) of women continued use of MHT after the intervention phase

CEE, conjugated equine estrogens; CHD, coronary heart disease; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.
Manson JE, et al. *JAMA.* 2013;310:1353–68.

WHI MHT trials: Outcomes by age group

Primary endpoints for the overall combined phases by 10-year age groups at randomization (13 years' cumulative follow-up)

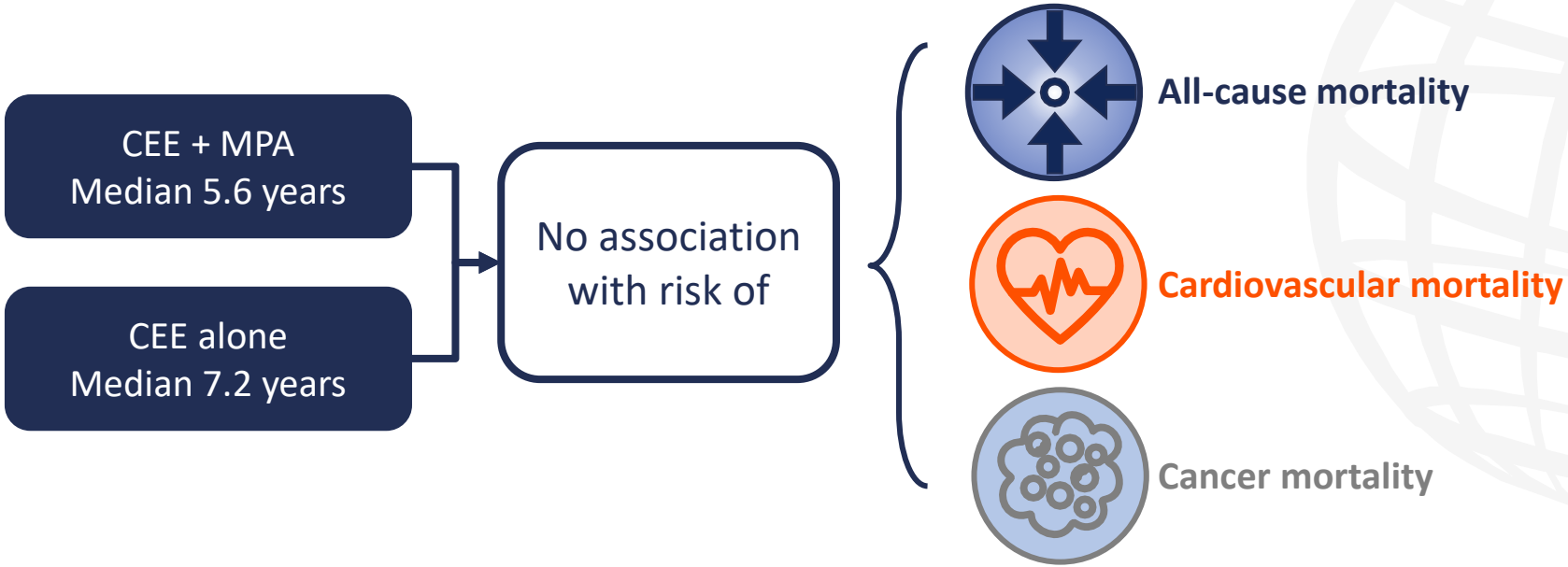
	CEE + MPA trial				CEE only trial			
	Events, n (annualized %)				Events, n (annualized %)			
	CEE + MPA n=8,506	Placebo n= 8,102	Difference /10,000 PY	HR (95% CI)	CEE n=5,310	Placebo n=5,429	Difference /10,000 PY	HR (95% CI)
CORONARY HEART DISEASE								
50–59 y	93 (0.26)	69 (0.21)	+5	1.27 (0.93–1.74)	42 (0.21)	64 (0.32)	-11	0.65 (0.44–0.96)
60–69 y	201 (0.44)	199 (0.46)	-2	0.97 (0.79–1.18)	183 (0.67)	188 (0.67)	0	1.00 (0.82–1.23)
70–79 y	193 (0.98)	162 (0.84)	+14	1.17 (0.95–1.44)	138 (1.03)	141 (1.03)	0	1.01 (0.80–1.28)
INVASIVE BREAST CANCER								
50–59 y	132 (0.37)	93 (0.28)	+9	1.34 (1.03–1.75)	46 (0.23)	61 (0.30)	-7	0.76 (0.52–1.11)
60–69 y	198 (0.43)	149 (0.34)	+9	1.27 (1.02–1.57)	80 (0.29)	105 (0.37)	-8	0.78 (0.58–1.05)
70–79 y	104 (0.53)	81 (0.42)	+11	1.25 (0.94–1.67)	42 (0.31)	50 (0.36)	-5	0.85 (0.56–1.28)

CEE, conjugated equine estrogens; CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; PY, patient-years; WHI, Women's Health Initiative; Y, years of age.

Manson JE, et al. *JAMA.* 2013;310:1353–68.

WHI long-term follow-up

- All-cause and cause-specific mortality after a cumulative 18-year follow-up



CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative.
Manson JE, et al. *JAMA*. 2017;318:927–38.

MHT provides effective symptom control, but…

- Early termination of CEE + MPA trial in 2002 because of **increased breast cancer risk** and an unfavourable risk–benefit ratio vs placebo
- Early termination of CEE trial in 2004 because of **increased stroke incidence** not offset by lower CHD risk in the hormone group vs placebo

Did the timing of MHT after natural menopause affect these results?

CEE, conjugated equine estrogens; CHD, coronary heart disease; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate.
Manson JE, et al. *JAMA.* 2013;310:1353–68.

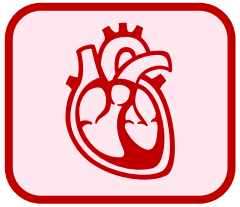
Kronos Early Estrogen Prevention Study (KEEPS)

- Primary research question: does MHT started within 3 years of natural menopause slow the progression of subclinical atherosclerosis in women without pre-existing CVD?
- Choice of MHT was dictated by local guidelines but was based on using 'the lowest dose'
  - Both oral CEE (0.45 mg/d) and transdermal (17β-estradiol; 50 µg/d) estrogens were investigated in combination with cyclical micronized progesterone (oral; 200 mg/d for the first 12 days of the month)

CAC, coronary artery calcium; CEE, conjugated equine estrogens; CIMT, carotid artery intima-media thickness; CVD, cardiovascular disease; MHT, menopausal hormone therapy.
Miller VM, et al. *Menopause.* 2019:26:1071–84.

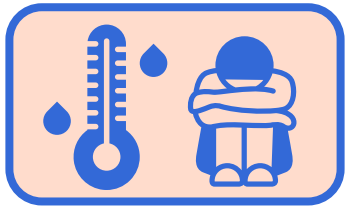
KEEPS: Selected outcomes with MHT

- Cardiovascular effects of MHT

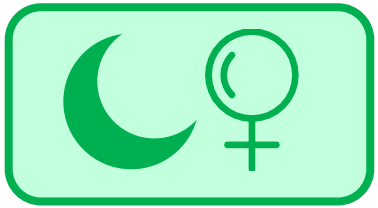


  - Neutral effect on rate of change in CIMT and systolic blood pressure
  - Nonsignificant trend toward reduction in CAC

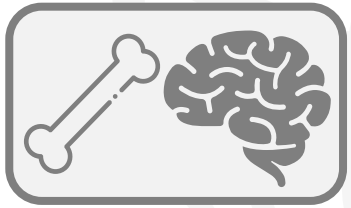
- Menopausal symptoms with MHT



  - Decreases in hot flushes and night sweats
  - Decreased depression and anxiety



  - Improvement in some sleep domains
  - Improvements in physical and emotionally related sexual function (greater with transdermal than oral MHT)



  - Bone mineral density maintained
  - No adverse effects on cognition

CAC, coronary artery calcium; CIMT, carotid artery intima-media thickness; KEEPS, Kronos Early Estrogen Prevention Study; MHT, menopausal hormone therapy.
Miller VM, et al. *Menopause.* 2019:26:1071–84 .

KEEPS: Summary and conclusions

Oral CEE and transdermal E2: Similarities

- Favourable effects on vasomotor symptoms, sexual function, QoL, bone density
- Neutral effects on blood pressure (adverse effect in WHI)
- Generally favourable or neutral effects on cardiovascular biomarkers (but differences related to first-pass liver metabolism)
- Neutral effects on CIMT and CAC (non-significant trend for the latter)
- Neutral effects on cognition (adverse effect in WHI, age >65)

Oral CEE and transdermal E2: Differences

- Oral CEE improved mood
- Transdermal E2 improved HOMA-IR and had some advantages for sexual function

KEEPS highlights the need for individualized decision making for MHT, given the different treatment priorities and risk-factor statuses of different women.

Additional research on MHT in newly menopausal women is needed, including different formulations/doses/routes of delivery.

CAC, coronary artery calcium; CEE, conjugated equine estrogens; CIMT, carotid artery intima-media thickness; E2, estradiol; HOMA-IR, homeostasis model assessment of insulin resistance; KEEPS, Kronos Early Estrogen Prevention Study; MHT, menopausal hormone therapy; QoL, quality of life; WHI, Women's Health Initiative.

Miller VM, et al. *Menopause.* 2019:26:1071–84.

touch ENDOCRINOLOGY®

Early versus Late Intervention Trial with Estradiol (ELITE)

643 healthy postmenopausal women, stratified by:
- <6 years since menopause (Early group)
- ≥10 years since menopause (Late group)

→

Randomized, placebo-controlled trial: oral 17β-estradiol daily (plus cyclical progesterone vaginal gel if uterus intact)

→

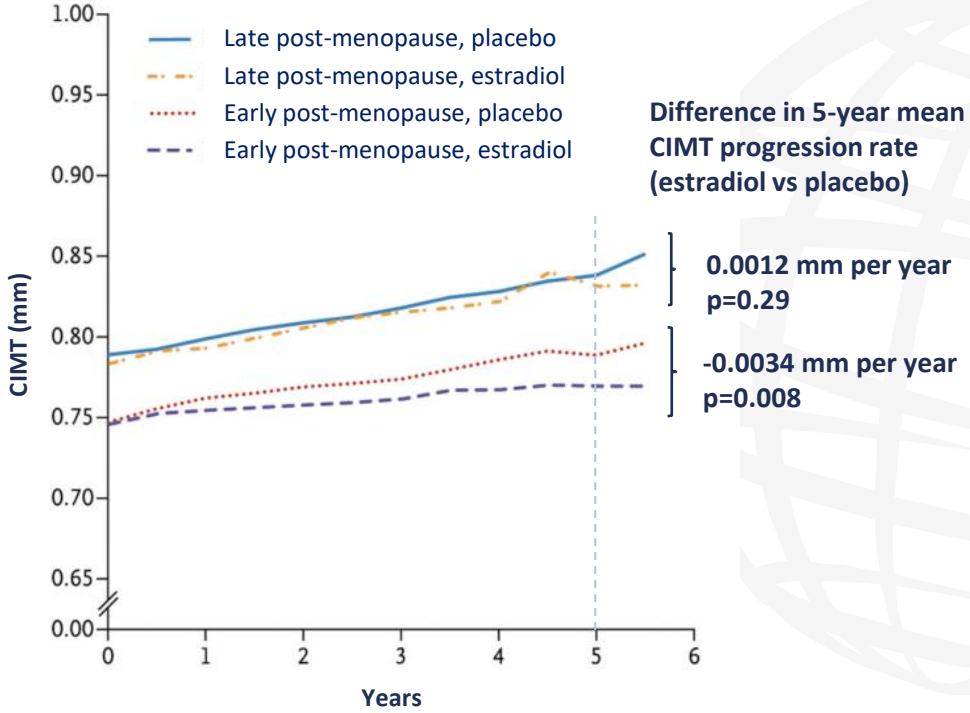
Primary outcome
- Change in CIMT, measured every 6 months

CIMT, carotid artery intima-media thickness.

Hodis HN, et al. *New Engl J Med.* 2016:374:1221–31.

ELITE: Outcomes

- After 5 years, rate of CIMT progression was lower with MHT vs placebo, but only in the early post-menopause group
- Similar results with or without vaginal progesterone
- Similar results with or without lipid-lowering or antihypertensive therapy
- No differences between treatment groups in CT measurement of coronary atherosclerosis



CIMT, carotid artery intima-media thickness; CT, computed tomography; ELITE, Early versus Late Intervention Trial with Estradiol; MHT, menopausal hormone therapy.
Hodis HN, et al. *New Engl J Med.* 2016:374:1221–31.
From *N Engl J Med*, Hodis HN, et al., Vascular effects of early versus late postmenopausal treatment with estradiol, 374, 1228. Copyright © (2021) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

ELITE: Support for the timing hypothesis

Women starting MHT within 6 years of menopause showed a significant slowing of subclinical carotid artery atherosclerosis; those ≥10 years post-menopause showed no difference.

MHT reduced early atherosclerosis but not established lesions.

No difference in adverse events between treatment groups.

Agreement with the literature: Women who are young and/or in close proximity to menopause when starting MHT have reduced coronary heart disease and overall mortality.

ELITE, Early versus Late Intervention Trial with Estradiol; MHT, menopausal hormone therapy.

Hodis HN, et al. *New Engl J Med.* 2016:374:1221–31.

CV summary: WHI, KEEPS and ELITE

	WHI[1]	KEEPS[2,3]	ELITE[4]
Population	• Mean age: 63 years old • 2–3% prior MI • 4–8% angina	• Mean age: 53 years old • ≤3 years from menopause • No subclinical coronary atherosclerosis	• Median age: 55 years (early [<6 years]) • Median age: 64 years (late [>10 years]) • No evidence of CVD
Active treatments	• oCEE (0.625 mg/day) ± oMPA	• oCEE (0.45 mg/d) ± oP* or tE (50 µg/d)± oP*	• oE (1 mg/day) ± vP*
CV findings	• Increased risk of stroke during treatment (but not post-treatment follow-up) • Overall lower risk of MI in women <10 years from menopause	• No difference in subclinical atherosclerosis progression	• Early: lower rate of CIMT progression • Late: no difference in rate, overall higher CIMT than early group

*Administered on a cyclical schedule rather than daily.

CEE, conjugated equine estrogens; CIMT, carotid intima-media thickness; CV(D), cardiovascular (disease); E, 17β-estradiol; MI, myocardial infarction; ELITE, Early versus Late Intervention Trial with Estradiol; KEEPS, Kronos Early Estrogen Prevention Study; MPA, medroxyprogesterone acetate; o, oral; P, progesterone; t, transdermal; v, vaginal; WHI, Women's Health Initiative.

1. Manson JE, et al. *JAMA.* 2013;310:1353–68; 2. Miller VM, et al. *Menopause.* 2019:26:1071–84; 3. Miller VM, et al. *J Cardiovasc Transl Res.* 2009;2:228–39.
4. Hodis HN, et al. *New Engl J Med.* 2016:374:1221–31.

Breast cancer risk with MHT: 20-year data

Meta-analysis of >100,000 women

Estrogen plus daily progestogen

- 20-year breast cancer incidence per 100 women aged 50–69[1]

Estrogen only

- 20-year breast cancer incidence per 100 women aged 50–69[1]

Million Women Study:[2]
>900,000 postmenopausal women

- 20-year breast cancer mortality rate ratio

	Current user: estrogen + progestogen	Current user: estrogen only	Past user
<5 years' MHT	1.39	1.15	0.99
≥5 years' MHT	1.64	1.35	1.24

MHT, menopausal hormone therapy.

1. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet.* 2019;394:1159–68; 2. Beral V, et al. *Lancet.* 2019;394:1139.

QResearch and CPRD database case control studies for risk of breast cancer with MHT

Two nested case control studies matching >98,000 women with breast cancer from 1998–2018 with >450,000 controls[1]

Long-term (≥5 years) MHT vs never use

- **OR 1.15** (95% CI 1.09–1.21) **Estrogen-only** MHT
- **OR 1.79** (95% CI 1.73–1.85) **Estrogen-progestogen** MHT

Highest risk: **norethisterone**
Lowest risk: **dydrogesterone**

Past **long-term estrogen-only** MHT or **short-term estrogen-progestogen** MHT → No increased risk

Past **long-term estrogen-progestogen** MHT → **OR 1.16** (95% CI 1.11–1.21)

Confounding factors and limitations[2]

- Breast cancer risk factors other than MHT not included
- Data integrity and comprehensiveness lower than for an RCT; not balanced for unknown confounders
- No information on past adherence or switching MHT
- No discrimination between continuous and switching, or oral and non-oral estrogens
- Included historical systemic MHT prescribing not representative of modern-day practice

CI, confidence interval; CPRD, Clinical Practice Research Datalink; MHT, menopausal hormone therapy; OR, adjusted odds ratio; RCT, randomised controlled trial.

1. Vinogradova Y, et al. *BMJ.* 2020;371:m3873; 2. Panay N, Davis S. 2020. IMS Statement on Use of Hormone Replacement Therapy and the Risk of Breast Cancer. Available at www.imsociety.org/manage/images/pdf/340bc1797dc687136cd14c2879c3d03a.pdf (accessed November 17, 2020).

touch ENDOCRINOLOGY®

IMS recommendations 2016: What is the benefit–risk ratio for MHT?

+

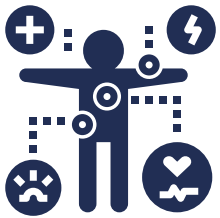
- MHT is the most effective treatment for vasomotor symptoms
- May also improve QoL, sexual function and other symptoms such as joint and muscle pains, mood changes, sleep disturbance and vulvovaginal atrophy
- Prevents bone loss; lowers risk of hip, vertebral and other osteoporosis-related fractures
- Decreased risk of MI and overall mortality if estrogen-only MHT initiated in women <60 years of age and/or within 10 years of menopause (less compelling for estrogen-progestogen MHT)

–

- Risks outweigh benefit if initiated in women >60 years of age or >10 years post-menopause
- Increased risk of VTE and ischaemic stroke after 60 years of age (probably lower with transdermal MHT)
- Risk of breast cancer associated with estrogen-progestin MHT in women >50 years of age without hysterectomy
  - Not routinely recommended for breast cancer survivors

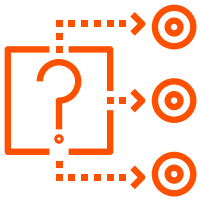
QoL, quality of life; MHT, menopausal hormone therapy; MI, myocardial infarction; VTE, venous thromboembolism.
de Villliers TJ, et al. *Climacteric.* 2016;19:313–5.

NAMS MHT Position Statement



The risks of MHT differ for women, depending on type, dose, duration of use, route of administration, timing of initiation and whether a progestogen is needed.

Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic re-evaluation.



MHT is a safe and effective option for the treatment of vasomotor symptoms and genitourinary syndrome of menopause, and the prevention of bone loss in healthy younger postmenopausal women, despite concerns about potential adverse CVD effects in older women.

CVD, cardiovascular disease; MHT, menopausal hormone therapy; NAMS, North American Menopause Society.

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. *Menopause.* 2017;24:728–53.

NAMS MHT Position Statement

Women <60 years or within 10 years of menopause onset with no contraindications:

- Benefit–risk ratio appears favourable for treatment of bothersome vasomotor symptoms and for those at elevated risk of bone loss or fracture
- Longer duration may be more favourable for ET than for EPT, based on the WHI RCTs

Women ≥60 years or initiating MHT more than 10–20 years from menopause onset:

- Benefit–risk ratio appears less favourable than for younger women because of greater absolute risks of CHD, stroke, VTE and dementia

CHD, coronary heart disease; EPT, estrogen-progestogen therapy; ET, estrogen therapy; MHT, menopausal hormone therapy; NAMS, North American Menopause Society; RCT, randomized controlled trials; VTE, venous thromboembolism; WHI, Women's Health Initiative.

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. *Menopause.* 2017;24:728–53.

Cochrane review including 22 clinical trials (>43,000 women)

Healthy women
50–60 years old

No contraindications:
Small absolute risk of harm with low-dose MHT

Hysterectomy:
Estrogen-only MHT for 5–6 years is relatively safe

MHT unsuitable if:
- Increased risk of CVD
- Increased risk of certain cancers (e.g. breast cancer in women with uterus)
- Increased risk of thromboembolic disease (transdermal may be safe)

Other considerations with MHT:
- NOT indicated for primary or secondary prevention of CVD, dementia or for preservation of cognitive function in postmenopausal women
- May prevent postmenopausal osteoporosis, but only recommended for women at significant risk who cannot take non-hormonal therapy
- Significantly increased risk of stroke and gallbladder disease
- Increased risk of coronary events, breast cancer, death from lung cancer and (in women >65 years of age) dementia with long-term use

CVD, cardiovascular disease; MHT, menopausal hormone therapy.
Marjoribanks J, et al. *Heart.* 2018;104:93–5.

MHT Summary

Individualized MHT provides effective relief of vasomotor and other menopausal symptoms, with options to reduce estrogen agonist effects[1]

- Safety may be a concern for women ≥60 years when starting MHT, or those starting MHT >10 years after menopause

Further investigation is needed in certain groups, including younger and perimenopausal women[2]

MHT, menopausal hormone therapy.

1. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. *Menopause.* 2017;24:728–53; 2. Marjoribanks J, et al. *Heart.* 2018;104:93–5.

Grey areas

- Women <50 years old
- Perimenopausal women
- Temporary or permanent iatrogenic ovarian failure

Marjoribanks J, et al. *Heart.* 2018;104:93–5.

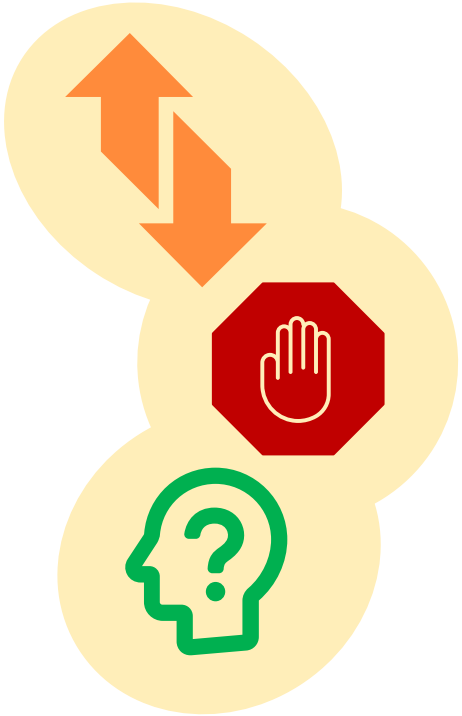
Beyond MHT: What non-hormonal alternatives are available for treating vasomotor symptoms in women going through menopause?

Prof. Dr. med. Petra Stute

Deputy Director,
Department of Gynecologic Endocrinology and Reproductive Medicine,
University Hospital of Bern,
Bern, Switzerland

touch ENDOCRINOLOGY®

MHT following the initial report of the WHI



- Increased interest in non-hormonal MHT alternatives after initial WHI findings[1]
- MHT initiation dropped from 8.6% to 2.8% ($p<0.001$), from 1996–2013 in the SWAN study,[2] with significantly fewer initiations based on:
  - HCP and friend advice, osteoporosis, heart disease, memory preservation, maintaining appearance
- Significant increases in MHT discontinuations due to media reports, HCP advice and worry relating to side effects and cancer[2]

HCP, healthcare professional; MHT, menopausal hormone therapy; SWAN, Study of Women's Health Across the Nation; WHI, Women's Health Initiative.

1. McGarry K, et al. *Clin Ther*. 2018;40:1778–86; 2.Crawford S, et al. *Menopause*. 2018;26:588–97.

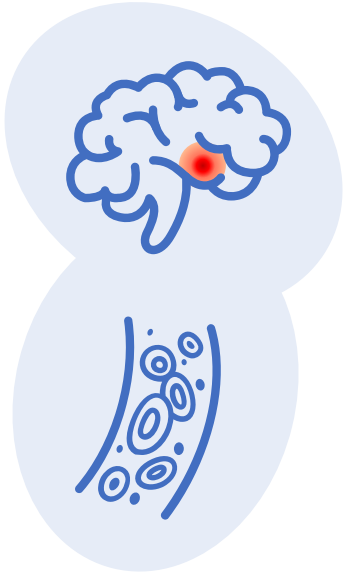
Pharmacological non-hormonal therapies

- SSRIs and SNRIs: thought to correct thermoregulation imbalance caused by estrogen deprivation and reduce the intensity and frequency of hot flushes by 20–65%

SSRIs 	Paroxetine	Only FDA-approved SSRI/SNRI for moderate–severe hot flushes	**Avoid** in tamoxifen users
	Fluoxetine	Second-line options	**Avoid** in tamoxifen users
	Sertraline		Moderate CYP2D6 inhibitor
	Citalopram	First-line options	Can be used in tamoxifen users
	Escitalopram		
SNRIs 	Duloxetine	First-line options	Moderate CYP2D6 inhibitor
	Venlafaxine		Safest choice in tamoxifen users
	Desvenlafaxine		

FDA, US Food and Drug Administration; SNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
Biglia N, et al. *ecancer.* 2019;13:909.

Pharmacological non-hormonal therapies[1]

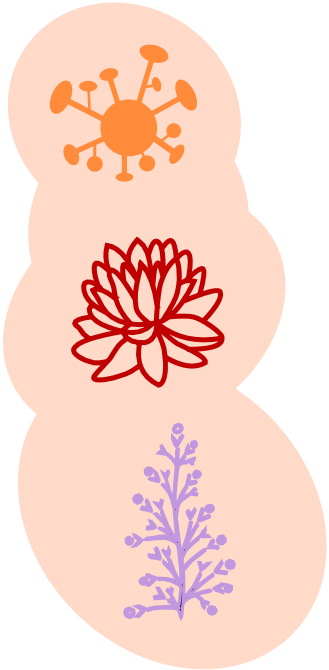


- Gabapentin and pregabalin: anticonvulsants which modulate thermoregulation at the hypothalamus
  - ~50% reduction in intensity and frequency of hot flushes
  - Mild–moderate efficacy in both healthy women and breast cancer survivors
  - May have more tolerability issues than SSRIs/SNRIs
- Clonidine: alpha-adrenergic antihypertensive that reduces peripheral vascular reactivity, and may inhibit hot flushes
  - Moderate efficacy in healthy women and breast cancer survivors
  - Significant side effects (hypotension, dizziness, xerostomia, constipation, potential hypertension if suddenly interrupted) which limit its use
  - Recommended in the UK for hot flushes and night sweats (not first line)[2]
- Oxybutynin: an anticholinergic which may also be an effective treatment

SNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

1. Biglia N, et al. *ecancer.* 2019;13:909; 2. National Institute for Health and Care Excellence. Menopause: diagnosis and management. 2015 (updated 5 December 2019). Available at: www.nice.org.uk/guidance/ng23 (accessed 22 January 2021).

Non-pharmacological non-hormonal therapies for hot flushes



Complementary and alternative medicines

- Purified pollen extract:[1] 'SSRI-like' activity; moderate reduction of hot flushes and improvement of other QoL parameters
  - No appreciable estrogenic effect or interaction with tamoxifen
- Soy and red clover isofavones:[2] similar in chemical structure to mammalian estrogens and bind to estrogen receptors, but with partial agonist and antagonist activity
  - Data limited by low-quality trials
- Black cohosh:[3] comparable efficacy to low-dose transdermal estradiol or tibolone reported, but no effect on estrogen-sensitive tissues, and no evidence of hepatotoxicity
  - Increased efficacy in combination with St. John's wort

QoL, quality of life; SSRI, selective serotonin reuptake inhibitor.

1. Fait T. *Drugs Context* 2019;8:212551; 2. McGarry K, et al. *Clin Ther*. 2018;40:1778–86;
3. Castelo-Branco C, et al. *Climacteric.* 2020; doi: 10.1080/13697137.2020.1820477 (Epub ahead of print).

Non-pharmacological non-hormonal therapies for hot flushes

- **Weight loss** – randomized controlled trials suggest that weight loss in overweight or obese women is associated with a reduction in hot flushes[1,2]
- **Yoga and exercise** – insufficient evidence[3]
- **Acupuncture** – some studies report a reduction in the frequency and/or severity of hot flushes versus no acupuncture/sham acupuncture[4]
- **Relaxation therapy** – insufficient evidence[5]
- **Cooling strategies** – efficacy not supported by scientific evidence[6]

1. Thurston RC, et al. *Menopause.* 2015;22:59–65; 2. Huang AJ, et al. *Arch Intern Med.* 2010;170:1161–7; 3. Daley A, et al. *Cochrane Database Syst Rev.* 2014;11:CD006108; 4. Befus D, et al. *J Altern Complement Med.* 2018;24:314–23; 5. Saensak S, et al. *Cochrane Database Syst Rev.* 2014;7:CD008582; 6. Biglia N, et al. *ecancer.* 2019;13:909.

touch ENDOCRINOLOGY®

Pathophysiology of vasomotor symptoms

- The exact mechanism of hot flushes is unknown

Abnormal hypothalamic thermoregulation → Vasodilation initiated in response to smaller increases in core temperature than normal →
- Increased blood flow and hyperthermia
- Profuse sweating and sensation of heat
- Peripheral vasodilation and chills

Associated with menopause and estrogen deficiency

BUT

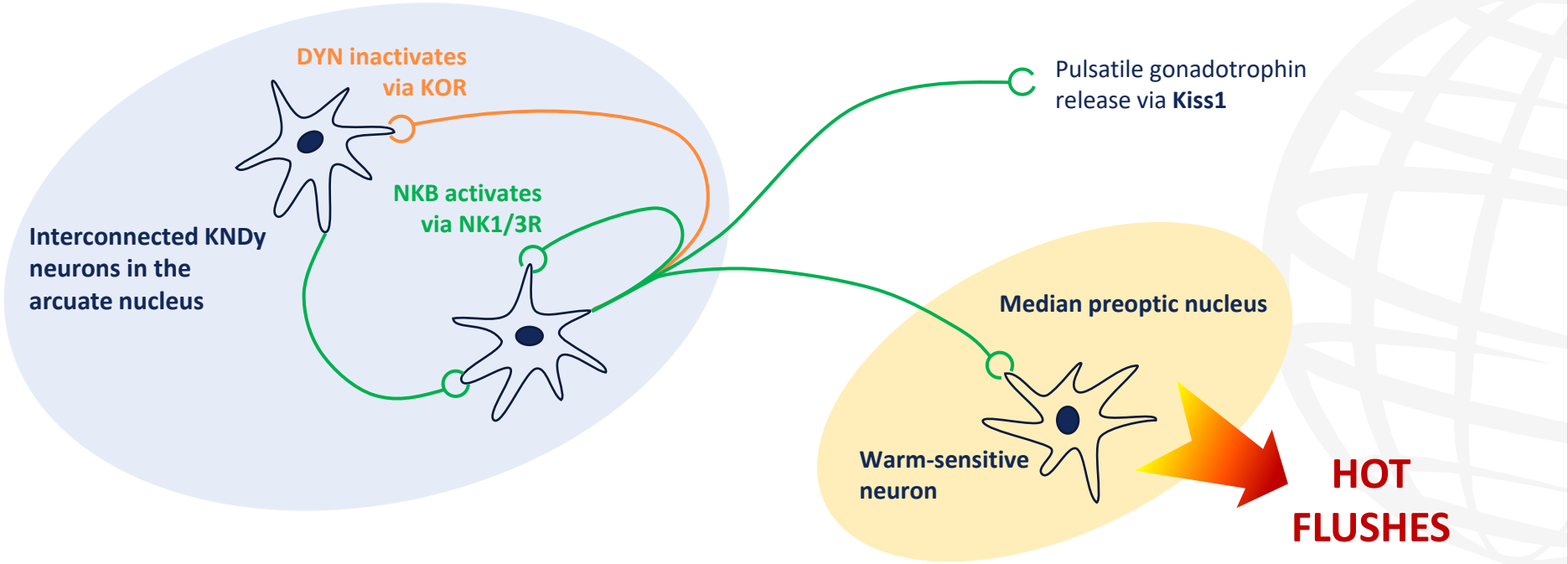
?
- Not related to estrogen levels
- Ceases over time with further declining estrogen – is rate of decline important?
- Priming of brain to react to estrogen withdrawal

Variety of treatment approaches
- Serotonin-norepinephrine axis
- Hypothalamic peptides: KNDy system controls gonadotrophin secretion and hypothalamic thermoregulation
- Calcitonin gene-related peptide

KNDy, kisspeptin, neurokinin B and dynorphin.

Bansal R and Aaggarwal N. *J Mid-life Health.* 2019;10:6–13.

KNDy neurons and thermoregulation

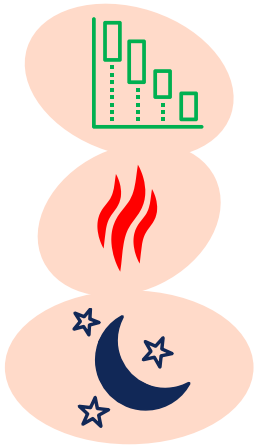


DYN, dynorphin; Kiss1, kisspeptin 1; KNDy, kisspeptin-neurokinin B-dynorphin system; KOR, κ-opioid receptor; NK(1/3)R, neurokinin (1/3) receptor; NKB, neurokinin B.
Reed SD. North Am Menopause Soc Annual Meeting 2018; Plenary Symposium #4.

touch ENDOCRINOLOGY®

Investigational KNDy agents: NT-814

- Dual NK1R and NK3R antagonist with oral once-daily dosing
- Significant reductions from baseline vs placebo in a 14-day, phase IIa, dose-finding trial



Frequency of hot flushes	150 mg/day: -4.9/day ($p<0.001$)
Daily severity score*	150 mg/day: -12.3 points ($p<0.001$)
Frequency of night-time awakenings	150 mg/day: -2.2/night ($p=0.002$)

- Symptom reduction apparent from week 1
- Well tolerated with an effect size vs placebo similar to that for MHT
- A phase IIb study is ongoing with treatment over 12 weeks

*(number of mild hot flushes x 1) + (number of moderate hot flushes x 2) + (number of severe hot flushes x 3).
KNDy, kisspeptin-neurokinin B-dynorphin system; MHT, menopausal hormone therapy; NK(1/3)R, neurokinin (1/3) receptor.
Trower M, et al. *Menopause*. 2020;27:498–505.

Investigational KNDy agents: Fezolinetant

- Oral NK3R antagonist investigated in a placebo-controlled, dose-ranging, phase IIb trial
- Significant improvements in frequency and severity of VMS at weeks 4 and 12 vs placebo, with the largest improvements seen at the highest dose (90 mg BID):

Frequency of moderate/severe VMS

Week 4: -3.5/day ($p<0.0001$)
Week 12: -2.6/day ($p=0.0005$)

Moderate/severe VMS severity score*

Week 4: -1.0/day ($p<0.0001$)
Week 12: -0.6/day ($p=0.0028$)

- Rapid improvement in symptoms vs placebo across all doses investigated
- Well tolerated
- Phase III investigation underway (NCT04003155)

*[(number of moderate VMS x 2) + (number of severe VMS x 3)]/(number of moderate + severe VMS).
BID, twice daily; NK3R, neurokinin 3 receptor; VMS, vasomotor symptoms.
Fraser GL, et al. *Menopause*. 2020;27:382–92.

Investigational agents: Other mechanisms

PH80-HF[1]

- Pherine nasal spray, administered six times daily, with rapid onset of action (35–65 s)
- Significantly improved the severity of daily hot flushes in a phase II exploratory trial

FP-101[2]

- Undisclosed mechanism of action, repurposed from an undisclosed indication
- Phase IIa study complete in 112 women, including women taking tamoxifen, but data yet to be released

1. Pherin Pharmaceuticals. Available at: www.pherin.com/hormone-replacement-therapy.html (accessed 22 January 2021); 2. PRNewswire. Available at: www.prnewswire.com/news-releases/new-potential-treatment-option-for-hot-flash-relief-for-menopausal-women-and-women-taking-tamoxifen-300811984.html (accessed 22 January 2021).

Summary

Choice of therapy for menopausal vasomotor symptoms depends on individual factors

Severity and frequency of symptoms, and quality of life priorities

Suitability for MHT and risk factors for breast cancer and cardiovascular events

Personal preference for hormonal or non-hormonal therapy

Comorbidities and other prescribed medication

MHT, menopausal hormone therapy.

touch ENDOCRINOLOGY®

Beyond a one-size-fits-all approach: How can we make personalized care a reality for women going through menopause?

Case-based discussion

touch ENDOCRINOLOGY®

Cases for discussion

- 51-year-old with a history of breast cancer
- 55-year-old with an increased CV risk
- 48-year-old with endometriosis
- 39-year-old with cervical cancer

CV, cardiovascular.

Clinical case 1: 51-year-old, history of breast cancer

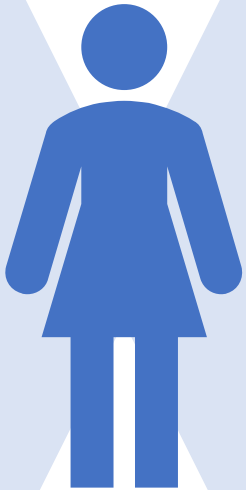
Patient history

BREAST CANCER

- Diagnosed age 45
- Early-stage, HR-positive, HER2-positive
- Tx: surgery + adjuvant trastuzumab, tamoxifen, letrozole

MENSTRUAL HISTORY

- Reducing bleeding frequency over past 8 months
- Last bleed was 2 months ago



Presenting complaints

COGNITION

- Poor memory
- Difficulty concentrating

NIGHT SWEATS

- Profuse sweating at night
- Disturbing sleep

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Tx, treatment.

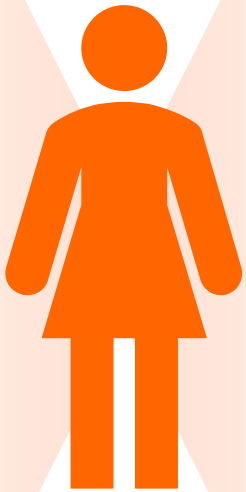
Clinical case 2: 55-year-old with increased CV risk

Patient history

MENSTRUAL HISTORY
- Menarche age 14
- Last menstrual bleed age 53

WEIGHT
- BMI of 32 kg/m^2
- Tried weight loss plans

TYPE 2 DIABETES
- Controlled with metformin
- HbA1c of 41 mmol/mol (5.9%)



Presenting complaints

HOT FLUSHES
- Frequent during the day
- Night sweats

JOINT PAIN
- Stiffness and aches

PREFERENCES
- Afraid of taking MHT
- Has read negative things about it online
- Wants to discuss alternatives

BMI, body mass index; CV, cardiovascular; HbA1c, haemoglobin A1C; MHT, menopausal hormone therapy.

touch ENDOCRINOLOGY®

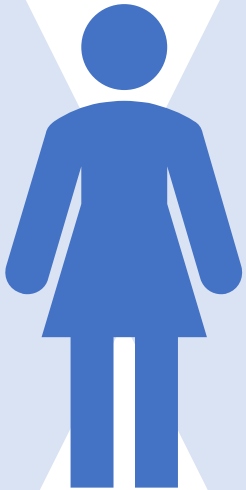
Clinical case 3: 48-year-old with endometriosis

Patient history

ENDOMETRIOSIS

- Dysmenorrhea since menarche
- Pelvic pain during menstruation
- Symptoms managed with a COC
- Difficulties with pregnancy (no children)

- Endometriosis diagnosed at age 47 years
- Benign mass in right ovary
- Bilateral oophorectomy without hysterectomy performed 6 months ago



Presenting complaints

HOT FLUSHES

- Frequent during the day
- Night sweats

INSOMNIA

- Difficulty sleeping
- Frequent waking

COC, combined oral contraceptive.

Clinical case 4: 39-year-old with cervical cancer

Patient history

CERVICAL CANCER

- Stage IB squamous cell cervical cancer
- Tx: radical hysterectomy and chemoradiation
- Tx initiated 2 months ago

EX-SMOKER

- 10 pack-year history

Presenting complaints

HOT FLUSHES

- Frequent during the day
- Night sweats

ANXIETY

- Sudden episodes of anxiety
- Worsened over recent weeks

Tx, treatment.