



Dr
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HRT update 2022

THE MENOPAUSE TRANSITION

- Vasomotor
- Irregular Bleeding
- Urinary Incontinence
- Sleep disturbance
- Dyspareunia
- Depression
- Anxiety
- Labile Mood
- Fatigue
- Headache
- Myalgias
- Arthralgias
- Weight gain
- Poor memory
- Dry Skin
- Dry eyes
- Vaginal Dryness
- Thin scalp hair
- Hirsutism



MENOPAUSAL HORMONE THERAPY in AUSTRALIA 2022

•OESTROGEN

- Oral tablet -oestrogen -for symptoms
- Gels or patches (oestrogen absorbed through the skin)
- creams and tablets (oestrogen) placed in the vagina

•PROGESTERONE

- a hormonal intrauterine device (IUD)(Mirena)
- Micronised (more natural) progesterone (Prometrium)
- Synthetic progesterones

MHT/HRT BENEFITS

MHT/HRT is usually helpful if you experience problems with hot flushes and night sweats. Mood, sleep and [sex drive problems](#) may also improve. Some women also say they find improvements in [joint aches](#), [vaginal dryness](#) and [incontinence](#).

MHT/HRT RISKS

The main risk is that some types of MHT lead to a slightly increased risk of developing breast cancer or thrombosis (blood clots in the legs or lungs). However, it can prevent other conditions such as osteoporosis, heart disease, fractures, diabetes and some types of cancers.

Current international recommendations:

The benefits outweigh the risks in women who are having significant symptoms from menopause, and that MHT is effective and safe for most healthy women.

Some side effects include fluid retention, bloating, breast tenderness and swelling, and irregular bleeding. These often go away with time.

Precautions include:

breast, endometrial cancer, hormone dependent cancer

- undiagnosed vaginal bleeding
- untreated uterine lining thickening
- raised risk of thrombosis
- coronary heart disease, stroke or dementia
- blood clots in the legs or lungs
- untreated hypertension (if you have high blood pressure that is treated, talk to your doctor about MHT)

Other risk factors: Talk to your own doctor about your medical history.

PIVOTAL STUDIES

- WHI (Women's Health Initiative) RCT 1993-2002
- PEPI (Post menopausal Estrogen/Progestin Interventions) 1989-94
- HERS (Heart and Estrogen Replacement) 1993-98
- NHS (Nurses Health Study)
- SWAN (Study of Women's Health Across the Nation) 1996-current
- MWS (Million Women Study) 1996- current
- WISDOM (Womens International Study of long Duration Estrogen after Menopause 1992-2002
- ELITE (Early Vs Late Intervention trial Estradiol) 2004-2013
- KEEPS (Kronos Early Estrogen Prevention Trial) 2005-2012
- Harvard mood study 1995-2006
- DOPS Danish Osteoporosis prevention Study 1990-2008

ISSUES TO ADDRESS

1. What is the effect of HRT on hot flushes, the genitourinary syndrome of menopause (also formerly known as vaginal atrophy) and other menopause symptoms?
2. What are the risks or risk reduction for osteoporosis, cardiovascular disease, breast, endometrial and colon cancer?
3. Does HRT slow the decline in cognitive function and prevent Alzheimer's disease?
4. What recommendations should women be given – what to take and for how long?

VASOMOTOR SYMPTOMS

I don't have hot flashes.

I have short, private
vacations in the
tropics.



your  cards
someecards.com

SLEEP DISTURBANCES

POOR SLEEP

- 45% Perimenopausal Women

CAUSES

- Hot Flashes
- Nocturia
- Anxiety
- Depression
- Primary Sleep Disorders



SLEEP DISTURBANCES

OESTROGEN in HYPOGONADAL WOMEN

- Improved sleep quality
- Improved length of REM sleep
- Improved latency (time from awake to sleep – the lightest of the non –REM sleep)

PRIMARY SLEEP DISORDERS

- Arousals in second half of night
- Look for other causes – apnoea, restless legs, anxiety and depression

DEPRESSION



- Harvard Study of Moods – depression during the menopausal transition
- SWAN (Study of Women's Health Across the Nation) – increased psychologic distress
- Depression more likely:
 1. Latter phases of perimenopause
 2. History of postnatal depression and PMDD
 3. Sleep disorders and hot flushes

DEPRESSION



- Treatment with transdermal oestradiol success
- KEEPS (Krono Early Prevention Study) :
- HRT can improve
 1. Depression
 2. Anxiety
 3. Sexual function
- Consider SSRI's

SEXUAL DYSFUNCTION

Hot flushing and night sweats – Menopausal Hormonal Therapy
Urogenital Syndrome of Menopause – Vaginal Oestrogen Creams.
Monalisa Laser – Fractional Co2 laser
Female Hypoactive Desire Disorder – Androfeme cream



OSTEOPOROSIS



- Oestrogen deficit results in increased osteoclast activity and bone resorption.
- Bone mass peaks third decade of life
- Accelerated loss starts 2 years before menopause and can continue for 2-4 years
- Oestrogen will reduce fractures by 65%'

OSTEOPOROSIS



WHI

- HRT vs placebo
 - RR 0.66 hip fracture
 - RR 0.66 vertebral fracture
 - RR 0.77 fragility fractures any site
-
- Consider alternatives to HRT if no other indication than primary prevention of osteoporosis
-
- Calcium and Vit D

CARDIOVASCULAR DISEASE



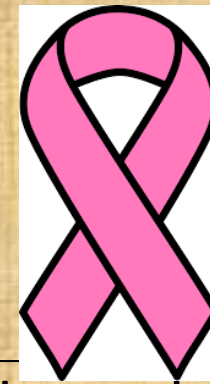
- Accounts for 30.7% of female deaths
- The lifetime risk of dying from ischaemic heart disease is 10 times that of risk of dying from:
 - Breast cancer
 - Reproductive cancer
 - Osteoporotic fracture
- American Heart Association does not recommend HRT to be used for primary prevention of heart disease

CARDIOVASCULAR DISEASE

- Observational and randomized studies suggest younger women starting HRT at menopause are **not** at increased risk
- KEEPS Study 2012
- DOPS Study 2012 (BMJ)
- Elite Study 2014 (younger women attenuation carotid intima-media thickness)



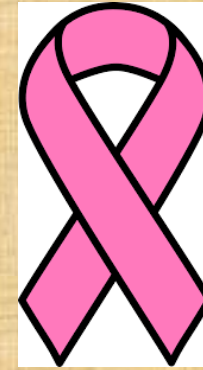
BREAST CANCER



- Oestrogen may promote pre-existing breast cancer
- Unknown if it will induce the growth of new cancers.
- Nurses' Health Study – slight increased risk
- WHI (CCE /MPA) combined HRT
 - Excess 8 cases /10 000 users per year
 - WHI (CCE alone) no increased risk

- Epidemiologic meta analysis of 21 Studies – increased risk over time
- Iowa Women's Health Study and other – no increased risk
- Million Women Study (observational) - increased risk

BREAST CANCER



- No randomized studies to evaluate different progestogens
- BRAC 1 and 2
 - Prophylactic oophorectomy
 - HRT improves quality of life
 - HRT does not increase risk of genetically determined breast cancer
- History of breast cancer avoid HRT
- Family history (first degree relative with pre-menopausal breast cancer)
 - HRT will not increase the risk

OVARY / COLON CANCER

No consistent risk with HRT has been demonstrated



ENDOMETRIAL CANCER

The lining should be suppressed (thin). Any thickening of the lining or bleeding must be investigated. Dr Burrows will discuss your circumstances and ways to take hormones in a safe manner.



THIN ENDOMETRIUM



ABNORMAL ENDOMETRIUM

NEUROLOGICAL FUNCTION & ALZHEIMER'S DISEASE

The effects of hormones on cognitive function varies enormously between trials with inconsistent outcome



Dr. Alois Alzheimer

VENOUS THROMBOEMBOLISM



- Evidence from RCT's – increased risk with current oral use on any HRT Vs Placebo
- Venous thromboembolism
 - -expensive to manage
 - -significant morbidity
 - -significant mortality
- Thus there is an important trade-off regarding risks and benefits of HRT.

VENOUS THROMBOEMBOLISM



- National Collaborating Centre for Women's and Children's Health concluded
 - Important Guidelines
1. Oral HRT increases VTE risk and can occur immediately (with or without progesterone)
 2. Transdermal HRT does not significantly increase this risk
 3. Risk increases substantially with age
 4. Risk discontinues when HRT stopped

STARTING HRT



ABSOLUTE CONTRAINDICATIONS

- hormone related cancer or active liver disease
- history of hormone – induced thromboembolism
- history of pulmonary embolism (not caused by trauma)
- undiagnosed vaginal bleeding
- pregnancy

MENOPAUSAL HORMONE THERAPY

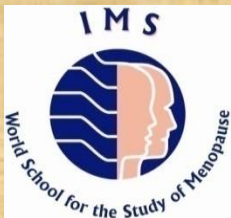
- MHT is the most effective treatment for moderate to severe menopausal symptoms and is most beneficial before the age of 60 years or within 10 years after menopause.
- ***The dose and duration of MHT should be consistent with treatment goals.***
- Estrogen only is appropriate therapy for women after a hysterectomy.
- Estrogen plus a progestogen should be used when the uterus is present.
- Topical low dose estrogen is preferred for those women whose symptoms are limited to vaginal dryness and dyspareunia.

IMS Recommendations. Baber et al Climacteric ;19: 109-150

Global Consensus Statement. De Villiers et al Climacteric 19:313-315)

Global Consensus Statement

- RCT and observational data provide strong evidence that estrogen only MHT may decrease coronary disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause
- *Data on estrogen – progestogen therapy in this population show a similar trend but with less precision*

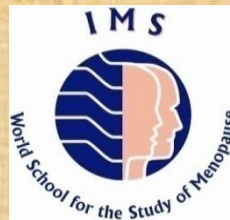


(Global Consensus Statement. De Villiers et al Climacteric 2016;19:313-315)

the risk of breast cancer in women over 50 years

Global Consensus Statement

- RCT and observational data provide strong evidence that estrogen only MHT may decrease coronary disease and all-cause mortality in women younger than 60 years of age and within 10 years of menopause
- *Data on estrogen – progestogen therapy in this population show a similar trend but with less precision*
- risk of breast cancer in women over 50 years associated with MHT is a complex issue but *is primarily associated with the addition of a progestogen to estrogen therapy and to the duration of use*



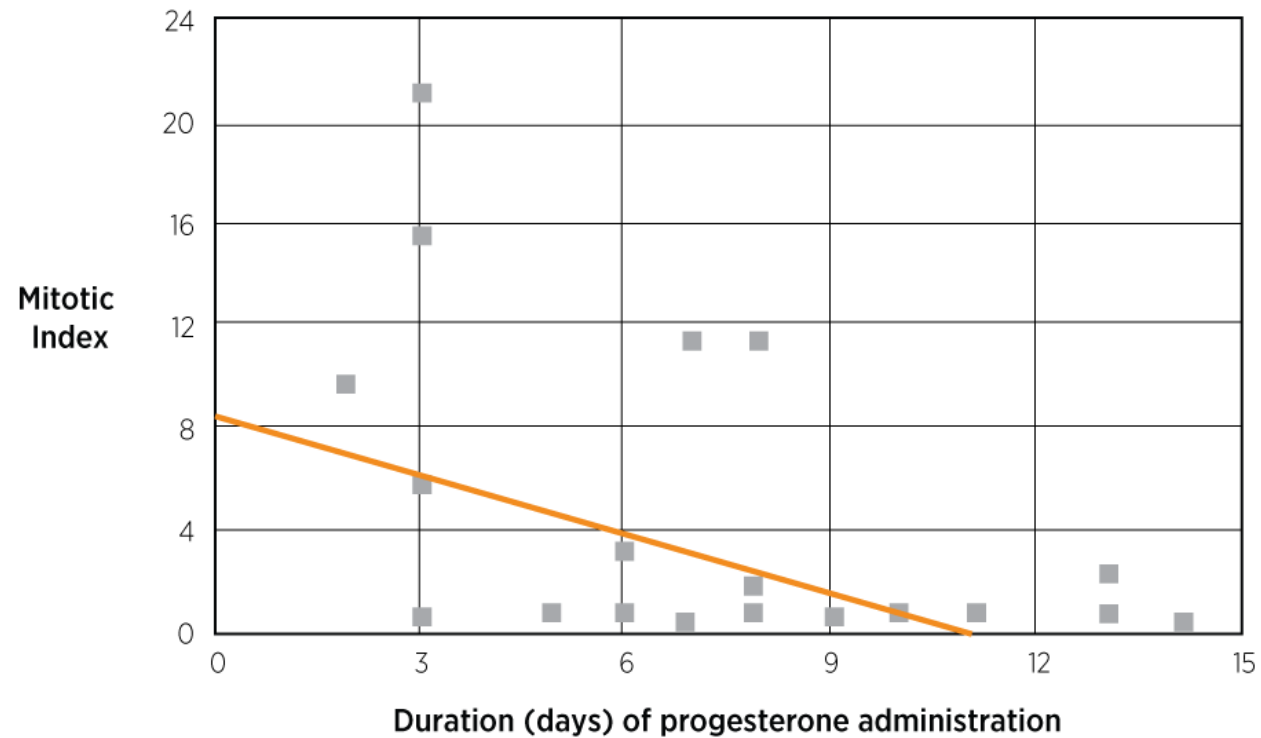
UPDATE ON THE USE OF
**Micronised
Progesterone:**
Hormone Replacement

Prometrium[®]
micronised progesterone



Anti-proliferative effects of progesterone

Regression of mitotic index compared with days of micronised progesterone administration.



Adapted from Moyer et al. *Fertil Steril* 1993

Achieving Endometrial Atrophy with Micronised Progesterone in Oestrogen Replacement Therapy

200 mg/day for 1st 12 days (PEPI 1996)
or
100 mg/day for days 1-25 (Darj et al 1991)



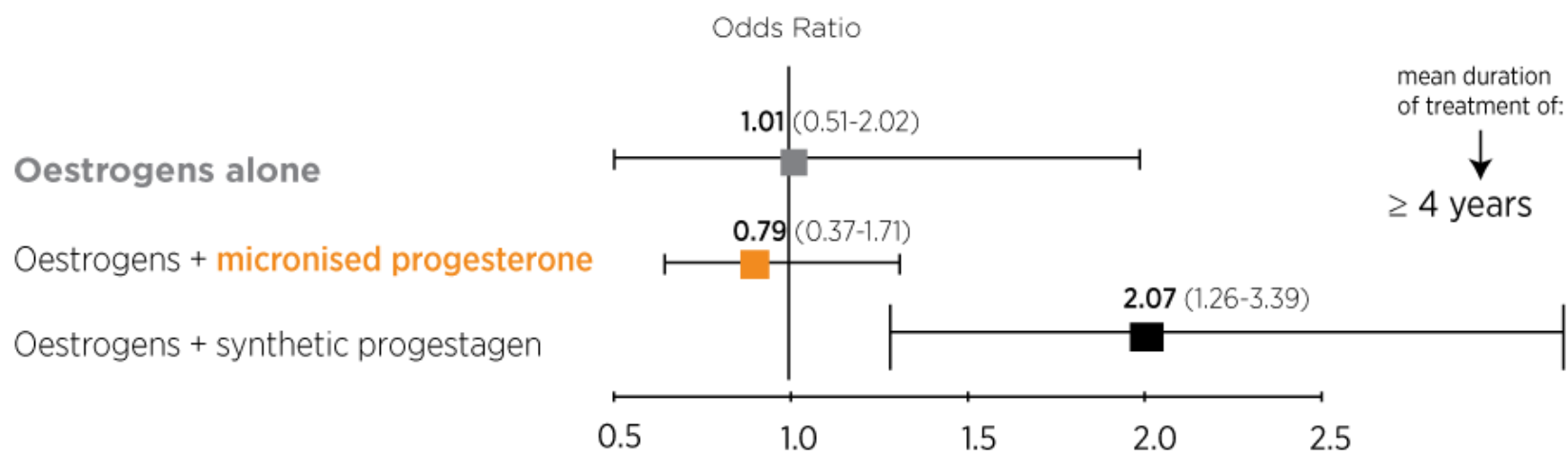
Endometrial atrophy (or quiescent)

Micronised Progesterone and Breast Safety



Breast Cancer Risk and HRT – CECILE Study

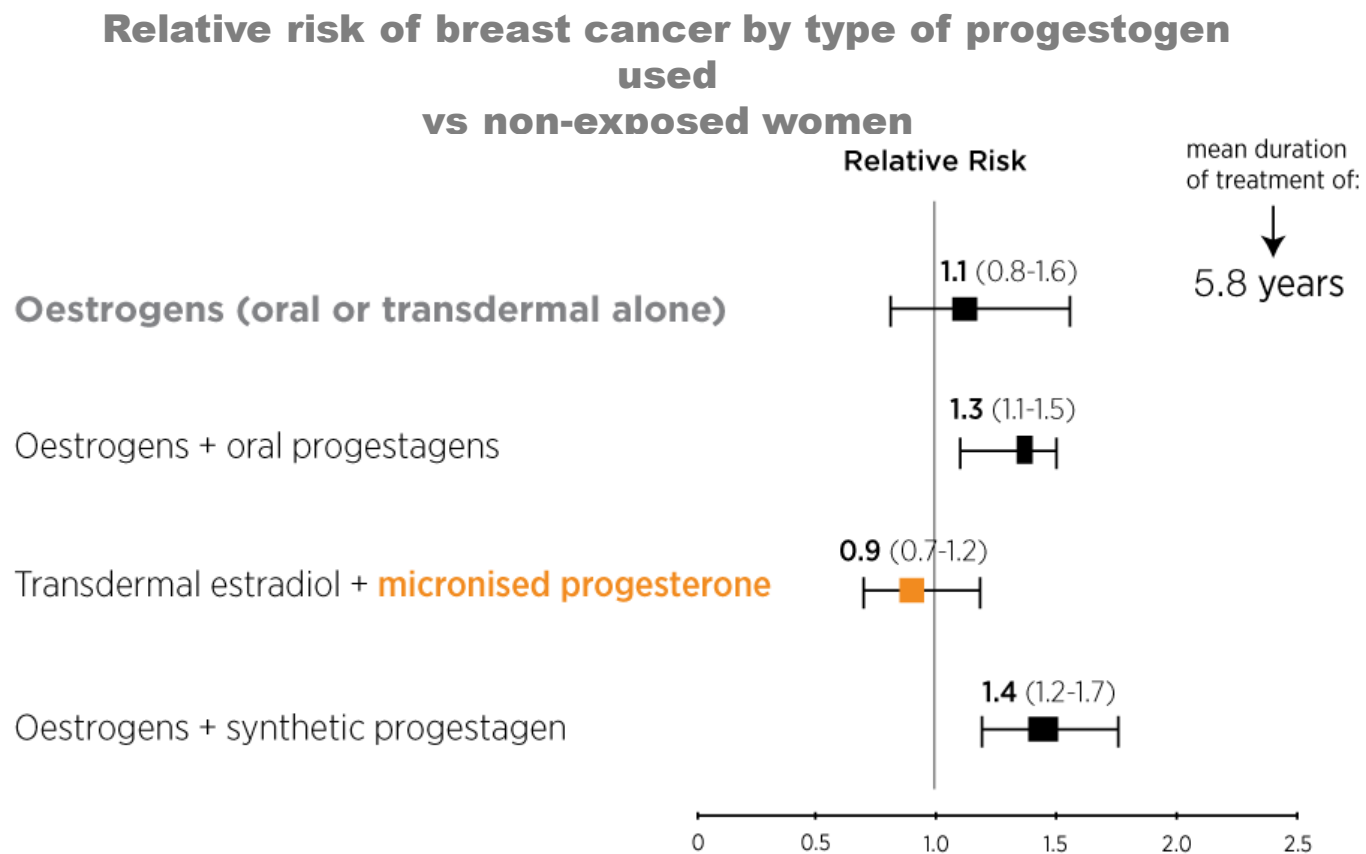
Odds ratios for breast cancer among current users of menopausal hormone therapy with treatment duration ≥ 4 years



Adapted from Cordina-Duverger E, PLoS One 2013

Odds ratios adjusted for study area / age at reference date / age at menarche / parity / age at first full-term pregnancy / breast feeding / history of benign breast disease / family history of breast cancer in first-degree relatives / BMI / oral contraceptive use

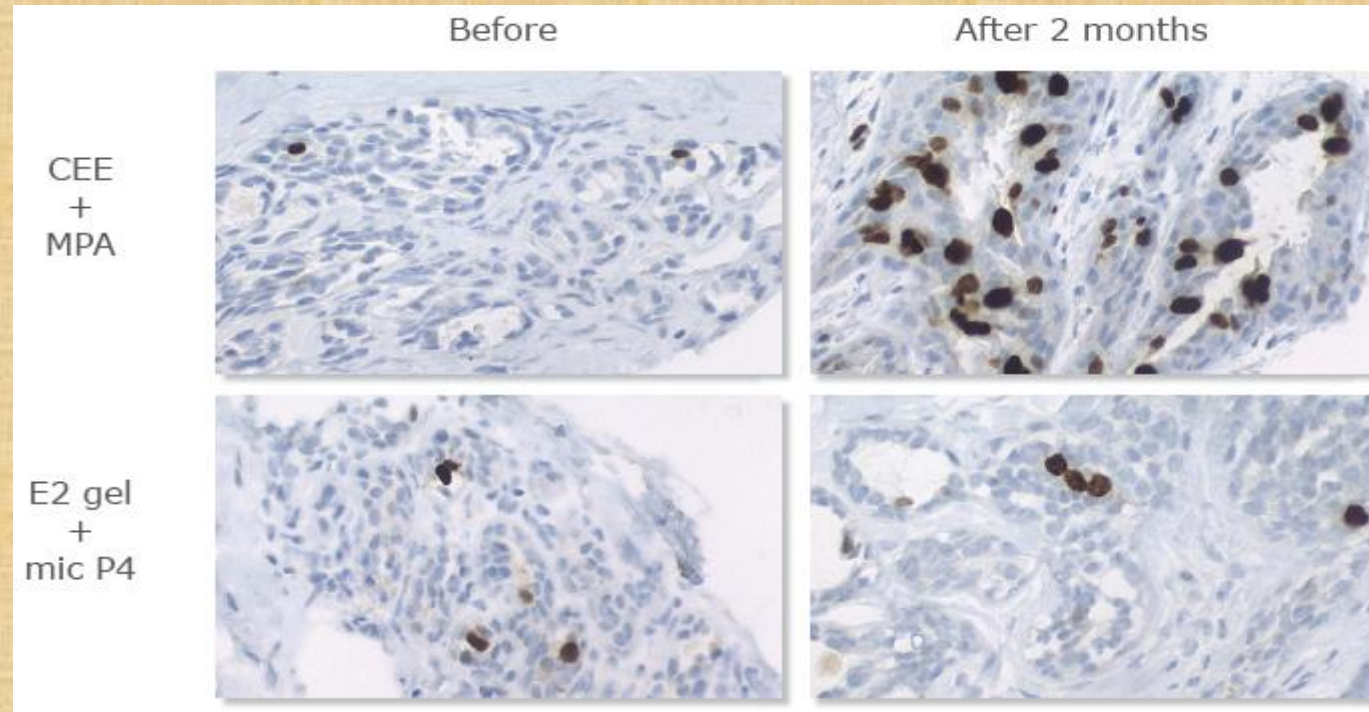
Breast Cancer Risk and HRT – E3N Study



The test for heterogeneity between micronised progesterone and synthetic progestins was significant ($p < 0.001$).

Adapted from Fournier A et al. 2005

Effects of percutaneous E2 - oral mic.P4 versus oral CEE + MPA on breast cell proliferation and bcl-2 protein in healthy women



Breast histologic findings from two individual women before (left) and after (right) 2 months of sequential treatment with either oral conjugated equine oestrogens–MPA (top) or percutaneous E2–oral micronised P (bottom). Nuclei of proliferating cells staining brown by Ki-67 MIB-1 antibody. (Original magnification X200)

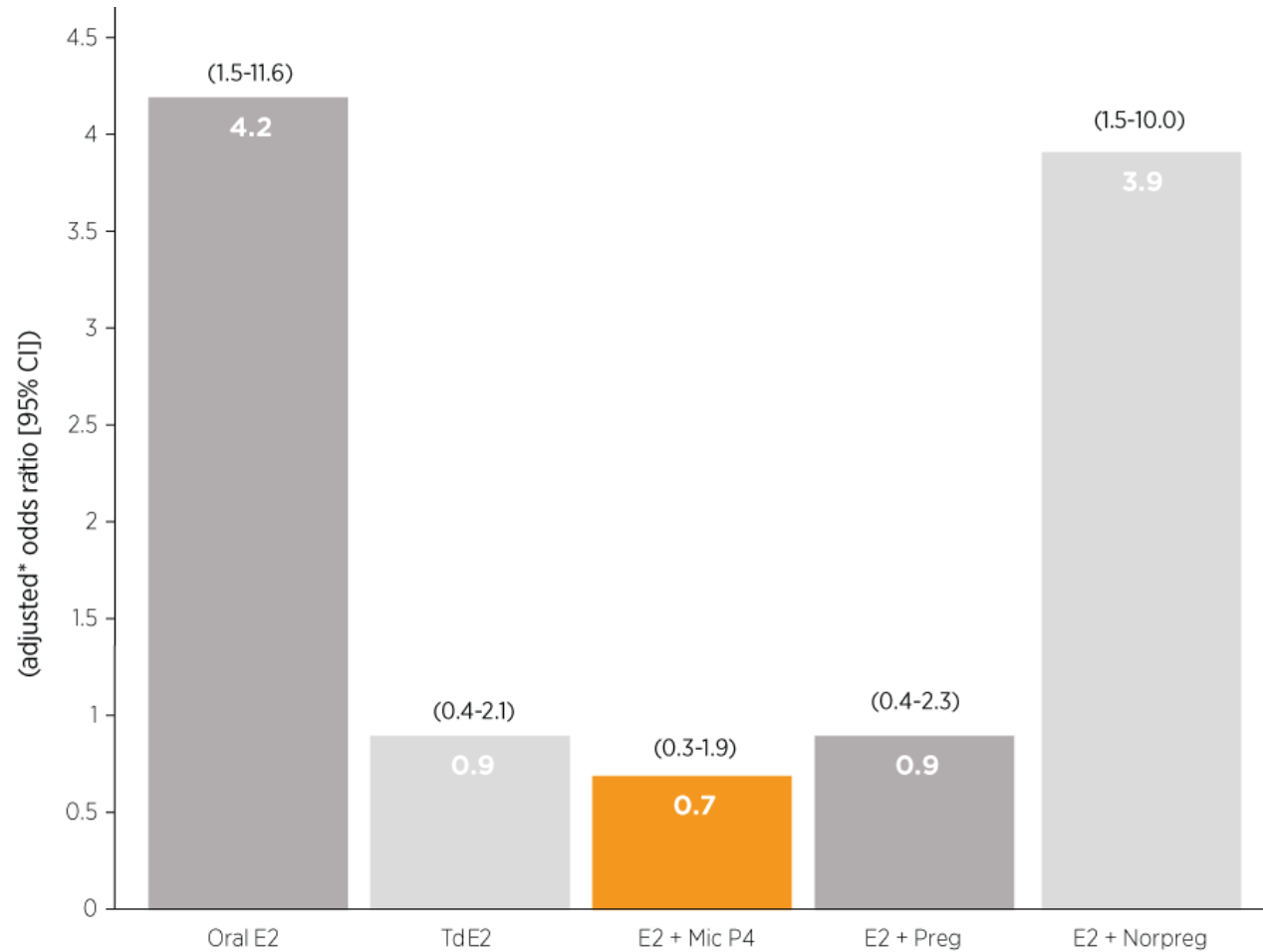
Breast cancer and progestogen: Guidelines

- “...It is not clear whether there is a class effect from the progestogen or whether the specific agent used influences breast cancer risk. Data from a large observational study suggest that **EPT with micronised progesterone carries a low risk of breast cancer with short-term use** (*meaning up to 5 years*) but carries an increased risk of breast cancer with all EPT formulations with long-term use.”¹
- “Emerging datareport that **progesterone** (and perhaps **dydrogesterone**) in combination with oestrogen does **not increase breast cancer risk** if given for 5 years or less.” (Level of Evidence C)²
- **A large European observational study** suggested that **micronised progesterone** or dydrogesterone used in association with oral or percutaneous estradiol may be associated with **a better risk profile** for breast cancer than synthetic progestogens.³
- The risk may be lower with micronised progesterone or dydrogesterone than with a synthetic progestogen.

Micronised Progesterone on VTE risk



Impact of Hormone Therapy on VTE Risk by Route of Oestrogen Administration and Type of Progestogens (ESTHER study)



*Adjusted for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy and cigarette smoking. Td E2 (Transdermal estradiol), Mic P4 (micronised progesterone), Preg (Pregnane derivatives), Norpreg (Norpregnanes derivatives)

Adapted from **Canonica M, et al.** *Circulation* 2007

**Postmenopausal Hormone Therapy and Risk of Idiopathic Venous
Thromboembolism. Results From the E3N Cohort Study**

Marianne Canonico, Agnès Fournier, Laure Carcaillon, Valérie Olié, Geneviève
Plu-Bureau, Emmanuel Oger, Sylvie Mesrine, Marie-Christine Boutron-Ruault,
Françoise Clavel-Chapelon and Pierre-Yves Scarabin

Arterioscler Thromb Vasc Biol published online Oct 15, 2009;

DOI: 10.1161/ATVBAHA.109.196022

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association,
7272 Greenville Avenue, Dallas, TX 75214

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ISSN: 1524-4636

Conclusions

"In this large study (from **E3N cohort study**), we found that route of oestrogen administration and concomitant progestogens type are two important determinants of thrombotic risk among postmenopausal women using hormone therapy.

Transdermal oestrogens alone or combined with progesterone might be safe with respect to thrombotic risk."



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This presentation is for general information and is not a substitute for a consultation with your general practitioner or Dr Burrows