폐경기간에 따른 HT의 방법:
치료방법의 변화/용량의 변화/사용 기간의 선택

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‘폐경기간’에 따른 HT

폐경 전후로 시작된 증상이 오랜 기간의 치료에도 중단 후 다시 치료가 필요할 정도로 여전히 불편

폐경 후 잘 지내다가 고령 **(65**세 이후**?)**이 되어서 치료가 필요할 정도의 불편

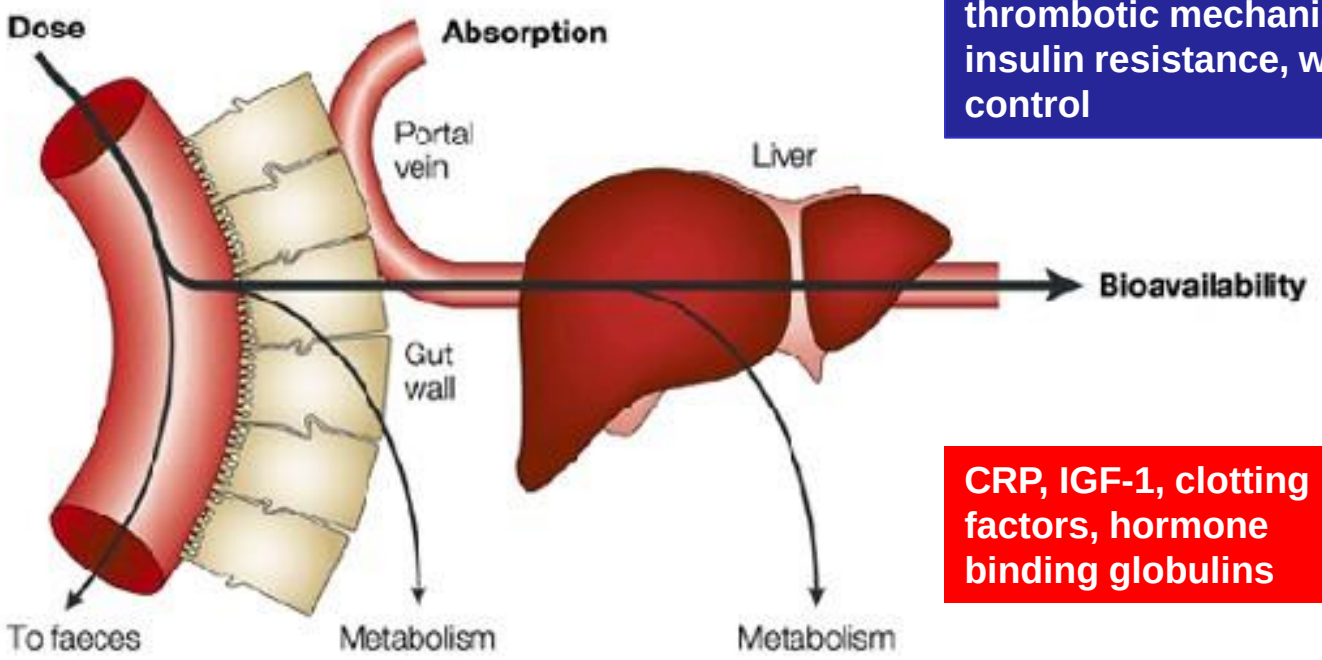
Methods

Use of estrogen: route

- **All routes of administration of ET can effectively treat menopausal symptoms**
  - **non-oral routes may offer both advantages & disadvantages**
  - **long-term benefit-risk ratio has not been demonstrated in RCTs with clinical outcomes**

- **There are differences related to,**
  - **the role of the first-pass hepatic effect**
  - **the hormone concentrations in the blood achieved by a given route**
  - **the biologic activity of ingredients**

Use of estrogen: route



Lipid metabolism, cardiovascular function, inflammatory & thrombotic mechanisms, insulin resistance, weight control

CRP, IGF-1, clotting factors, hormone binding globulins

Nature Reviews | Drug Discovery

Use of estrogen: non-oral

- **Transfer bioactive sex hormones directly into microcirculation of skin**

- **No first-pass hepatic transformation or deactivation of the dosed E (passive diffusion)**
  - **effective doses are therefore small**
    : doses are closer approximations of physiology than oral doses
  - **may not associated with adverse events**
  - **significant variations in the metabolism of oral E**
    : resulting in wide fluctuations in blood E levels

CHD

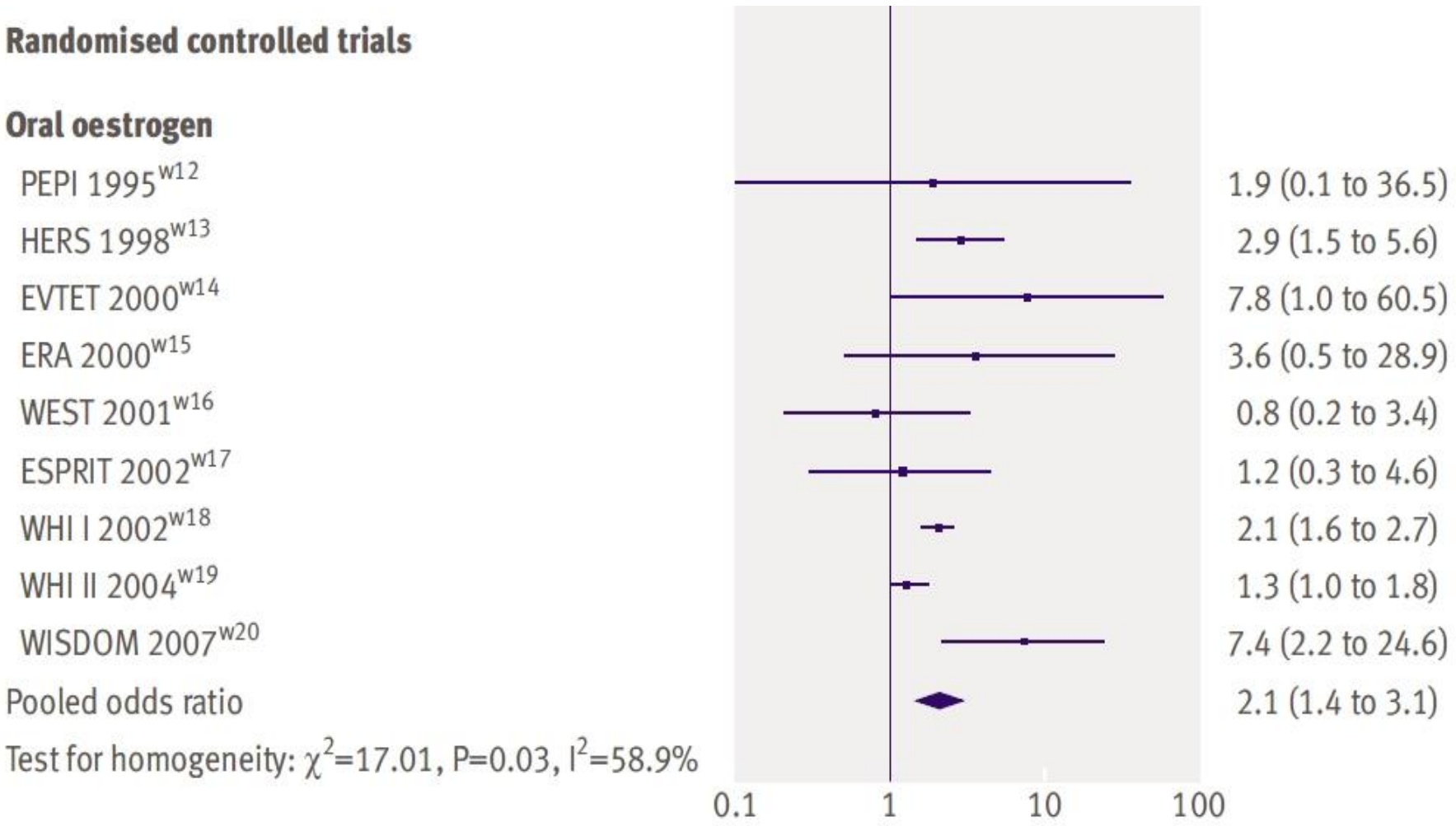
Risk of MI

HT Status	Age	Women-years	MI	Rate per 1000 women year	Crude RR	95% CI		Adjusted RR	95% CI	
Route[a] ($P < 0.0001$)										
Never any HT		2 082 277	3596	1.73	1.00			1.00		
Oral oestrogen		148 388	264	1.78	1.02	0.90	1.16	0.98	0.67	1.12
Dermal oestrogen		31 354	24	0.77	**0.61**	**0.41**	**0.91**	**0.62**	**0.42**	**0.93**
Oral combined		358 615	523	1.46	1.01	0.92	1.11	1.08	0.98	1.19
Dermal combined		25 196	23	0.91	0.82	0.54	1.23	0.95	0.63	1.43
Vaginal		68 723	69	1.00	**0.54**	**0.42**	**0.68**	**0.56**	**0.44**	**0.71**

- **N=698,098**
- **From a Danish national registry study**

Lokkegaard E, Eur Heart J 2008

Venous thromboembolism



Canonico M, BMJ 2008

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Venous thromboembolism

UK GPRD cohort

HRT exposure	Cases* n = 23 505	Controls* n = 231 562	Adjusted rate ratio (95% CI)†
No use‡	19 849 (84.4)	201 985 (87.2)	1.00 (Reference)
Tibolone	148 (0.6)	1651 (0.7)	0.92 (0.77–1.10)
Estrogen	1004 (4.3)	7851 (3.4)	1.32 (1.23–1.42)
Oral	729 (3.1)	5105 (2.2)	1.49 (1.37–1.63)
Patch	273 (1.2)	2721 (1.2)	1.01 (0.89–1.16)
Estrogen–progestogen	1375 (5.8)	10 420 (4.5)	1.48 (1.39–1.58)
Oral	1277 (5.4)	9342 (4.0)	1.54 (1.44–1.65)
Patch	92 (0.4)	1043 (0.5)	0.96 (0.77–1.20)
Progestogen	19 (0.1)	104 (0.0)	1.90 (1.14–3.17)
Past use	1107 (4.7)	9520 (4.1)	1.11 (1.04–1.19)

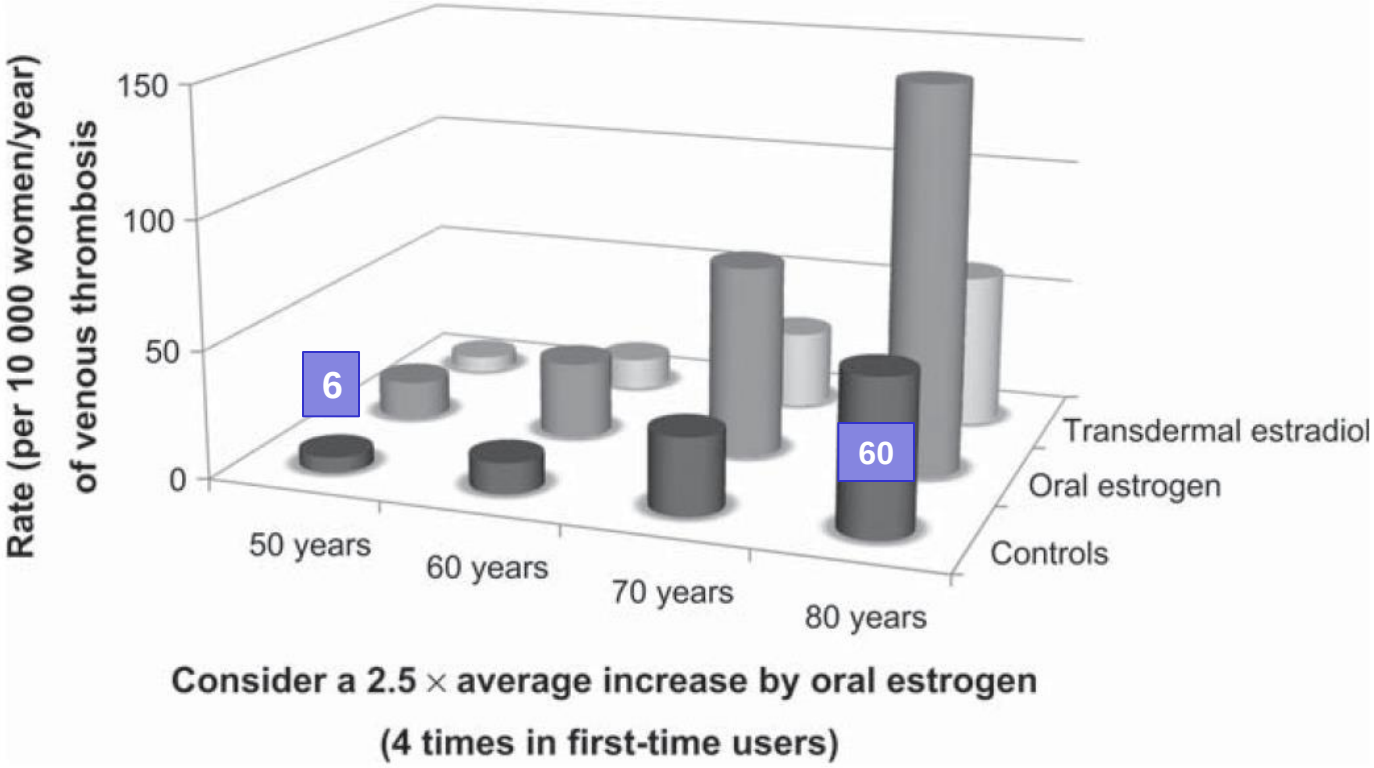
E3N cohort

	Hazard Ratios (95% Confidence Intervals)	
Treatment	Age-Adjusted	Multivariable Adjusted*
Never use	1 [reference]	1 [reference]
Past use	1.0 (0.7–1.3)	1.1 (0.8–1.5)
Current use of oral estrogens	1.5 (0.9–2.3)	1.7 (1.1–2.8)
Current use of transdermal estrogens	1.1 (0.7–1.6)	1.1 (0.8–1.8)

Renoux C, J Thromb Haemos 2010;
Canonico M, Arteriolscler Thromb Vasc Biol 2010

Venous thromboembolism

Absolute risk of VTE



Consider a 2.5 × average increase by oral estrogen

(4 times in first-time users)

L'Hermite M, Climacteric 2013

Stroke

PERSONAL PERSPECTIVE

Different mechanisms for benefit and risk of coronary heart disease and stroke in early postmenopausal women: a hypothetical explanation

Rogerio A. Lobo, MD[1] and Tom B. Clarkson, DVM[2]

Abstract

In younger postmenopausal women, estrogen is thought to be protective against coronary heart disease. The mechanism for this effect is likely to be an inhibition of the development of atherosclerosis. However, in older postmenopausal women with established atherosclerosis, the initiation of estrogen therapy may cause coronary artery plaque instability and rupture, resulting in coronary thrombosis and myocardial infarction. Compared with these findings of coronary disease prevention in younger women, estrogen therapy has been linked to an increased risk of ischemic stroke in both younger and older postmenopausal women, although the risk is small and the event rate in younger women is considered to be rare. Here, we provide an argument that the mechanism for stroke risk in younger women is not based on atherosclerotic disease, as occurs in older women for both coronary disease and stroke, but is related to thrombosis. Susceptibility for stroke is increased in women, and various factors leading to thrombosis may explain this risk. This notion is supported by data that estrogen regimens that decrease the risk of venous thrombosis (lower oral doses and transdermal therapy) may not be associated with an increase in ischemic stroke risk.

Key Words: Stroke – Coronary heart disease – Estrogen – Younger postmenopausal women – Atherosclerosis – Thrombosis – Hypothesis.

Lobo RA, Menopause 2011

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Stroke

UK GPRD cohort

Type of HRT	Cases* (n=15 710)	Controls* (n=59 958)	Rate ratio (95% CI)	
			Crude	Adjusted†
None	92.27 (14 496)	93.12 (55 834)	1.00‡	1.00‡
Transdermal route:	0.66 (103)	0.74 (441)	0.92 (0.74 to 1.14)	0.95 (0.75 to 1.20)
Oestrogen only	0.52 (81)	0.53 (317)	1.00 (0.78 to 1.28)	1.02 (0.78 to 1.34)
Oestrogen-progestogen	0.14 (22)	0.21 (124)	0.70 (0.45 to 1.11)	0.76 (0.47 to 1.22)
Oral route:	3.93 (618)	3.38 (2025)	1.20 (1.09 to 1.33)	1.28 (1.15 to 1.42)
Oestrogen only	1.67 (262)	1.34 (802)	1.28 (1.11 to 1.48)	1.35 (1.16 to 1.58)
Oestrogen-progestogen	2.27 (356)	2.04 (1223)	1.15 (1.02 to 1.31)	1.24 (1.08 to 1.41)

Type of HRT	Cases* (n=15 710)	Controls* (n=59 958)	Rate ratio (95% CI)	
			Crude	Adjusted†
None	92.27 (14 496)	93.12 (55 834)	1.00‡	1.00‡
Transdermal route:	0.66 (103)	0.74 (441)	0.92 (0.74 to 1.14)	0.95 (0.75 to 1.20)
Low dose (≤50 µg)	0.48 (76)	0.64 (384)	0.78 (0.61 to 1.00)	0.81 (0.62 to 1.05)
High dose (>50 µg)	0.17 (27)	0.10 (57)	1.87 (1.17 to 2.98)	1.89 (1.15 to 3.11)
Oral route:	3.93 (618)	3.38 (2025)	1.20 (1.09 to 1.33)	1.28 (1.15 to 1.42)
Low dose §	3.28 (515)	2.92 (1753)	1.16 (1.04 to 1.29)	1.25 (1.12 to 1.40)
High dose §	0.66 (103)	0.45 (272)	1.51 (1.20 to 1.90)	1.48 (1.16 to 1.90)

Renoux C, BMJ 2010

Stroke

Transdermal hormone therapy and the risk of stroke and venous thrombosis

L. Speroff

ml)[20]. Furthermore, individual women metabolize estrogen differently, depending on the route of administration, their own liver function, skin absorption, body composition, body size, potential medication interactions, and the presence of binding proteins, all of which contribute to individual variations in serum estradiol levels[19].

The only way to accurately compare clinical differences between oral and transdermal estrogen delivery is to establish that the two methods produce similar blood levels and that clinical differences reflect the first-pass effect through the liver. This is difficult to accomplish because the oral first-pass effect raises sex hormone binding globulin (SHBG) levels such that total serum estradiol levels are greatly affected. A study of 18 women showed that oral estrogen increased SHBG by 67% to 171%, whereas transdermal estrogen did not alter SHGB levels[21]. Estrogen-induced changes in SHBG may be clinically significant because estrogen unbound to SHBG determines the estrogen effects of a given regimen. The only study that measured free estradiol levels, compensating for increases in SHBG, showed

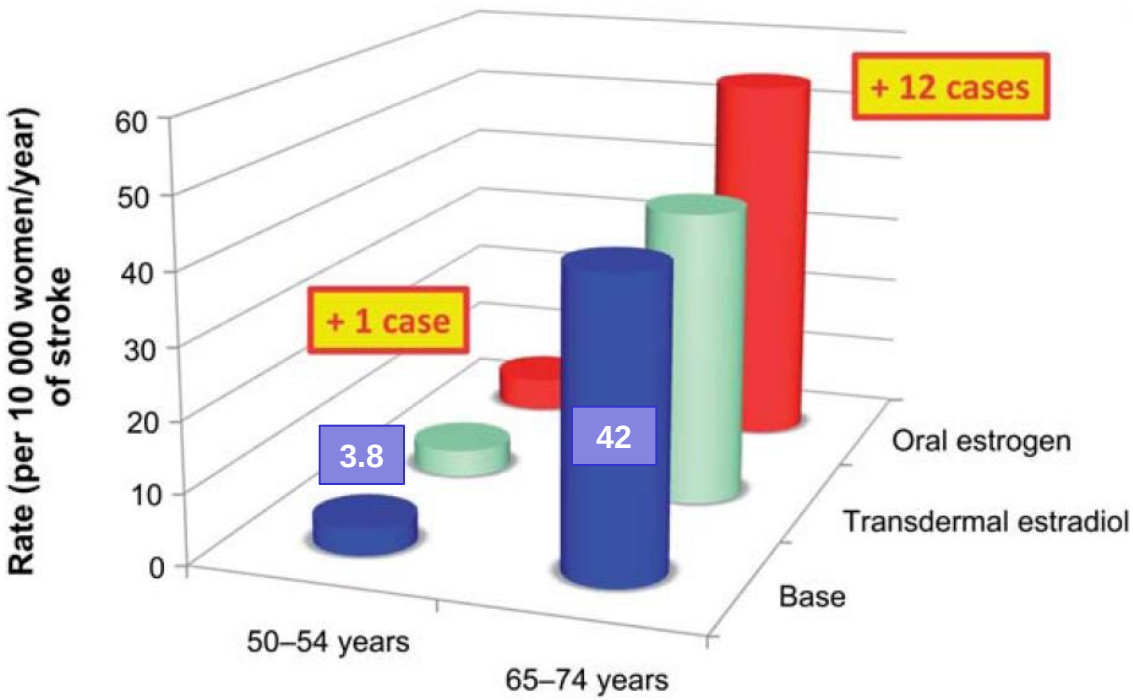
TAKE-HOME MESSAGE

What, in my view, is the clinical take-home message? Transdermal postmenopausal therapy is certainly an option for all patients, but it is the treatment of choice for women at high risk for venous thrombosis. In women with risk factors for stroke, it is prudent to use low doses of estrogen and to vigorously address the risk factors, such as effective treatment of hypertension. Would the transdermal route of administration be safer? This is an important question that cannot be definitively answered, but, because stroke risk is limited to ischemic events and it is possible that the transdermal route has a lower risk of thrombosis, it seems wise to promote this route of administration in older postmenopausal women and in women with risk factors for stroke. In addition, patients should not be given estrogen treatment after a vascular event in the expectation that recurrent vascular events would be prevented by the initiation of estrogen treatment. However, this recommendation is specifically targeted to women with existing vascular disease.

Speroff L, Climacteric 2010

Stroke

Absolute risk of thrombotic stroke events



For a 1.29 times increased risk by oral HRT and an 11 times increased basal risk from 50–54 to 65–74 years

L'Hermite M, Climacteric 2013

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Progesterone: VTE

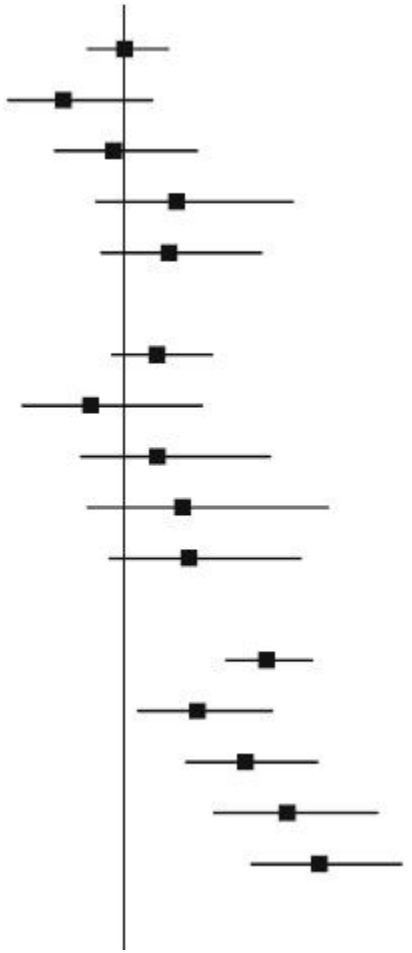
E3N cohort

Treatment	Hazard Ratios (95% Confidence Intervals)	
	Age-Adjusted	Multivariable Adjusted*
Never use	1 [reference]	1 [reference]
No progestogens use	…	…
Current use of micronized progesterone	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Current use of pregnane derivatives	1.3 (0.8–1.9)	1.3 (0.9–2.0)
Current use of norpregnane derivatives	1.7 (1.1–2.6)	1.8 (1.2–2.7)
Current use of nortestosterone derivatives	1.4 (0.8–2.5)	1.4 (0.7–2.4)

Canonico M, Arteriolscler Thromb Vasc Biol 2010

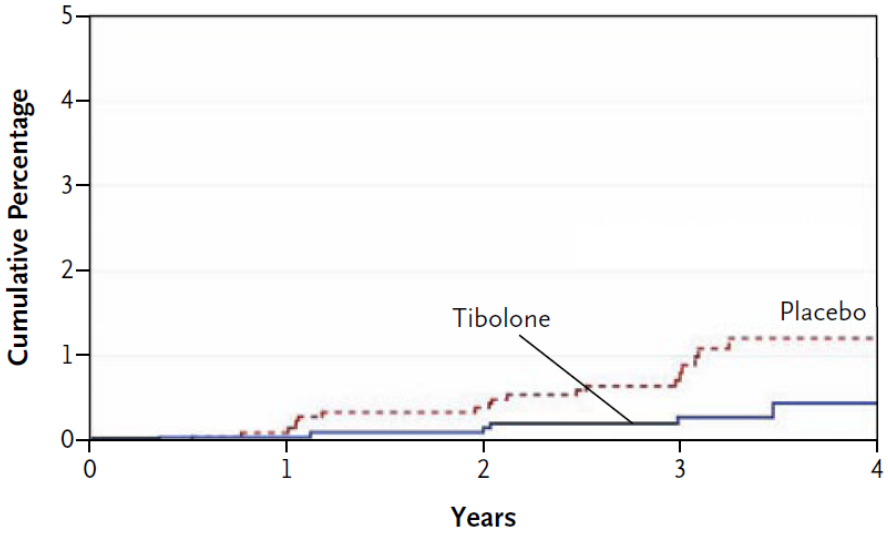
Progesterone: Breast cancer

HRT type and duration of exposure (years)	Cases/PY [a]	Relative risk [b] (95%CI)
Estrogen + progesterone	**129/40,537**	**1.00 (0.83-1.22)**
<2	18/8,697	0.71 (0.44-1.14)
[2-4[	33/11,647	0.95 (0.67-1.36)
[4-6[	30/7,619	1.26 (0.87-1.82)
6+	43/10,111	1.22 (0.89-1.67)
p for trend		0.04
Estrogen + dydrogesterone	**108/31,045**	**1.16 (0.94-1.43)**
<2	16/6,923	0.84 (0.51-1.38)
[2-4[	28/8,697	1.16 (0.79-1.71)
[4-6[	21/5,590	1.28 (0.83-1.99)
6+	35/7,876	1.32 (0.93-1.86)
p for trend		0.16
Estrogen + other progestagens	**527/104,243**	**1.69 (1.50-1.91)**
<2	86/22,792	1.36 (1.07-1.72)
[2-4[	134/30,189	1.59 (1.30-1.94)
[4-6[	106/19,942	1.79 (1.44-2.23)
6+	156/23,817	1.95 (1.62-2.35)
p for trend		0.01



Fournier A, Breast Cancer Res Treat 2008

Tibolone



- Random, double-blind, placebo-controlled
- Women with osteoporosis, 60~85 years
- N=4,538
- Tibolone 1.25 mg vs. placebo
- 3 years

Outcome	Tibolone (N = 2249)		Placebo (N = 2257)		Relative Hazard (95% CI)	P Value
	no. of events	*no. of cases per 1000 person-years*	*no. of events*	*no. of cases per 1000 person-years*		
New vertebral fracture	70	10.9	126	19.6	0.55 (0.41 to 0.74)	<0.001
Nonvertebral fracture‡	122	19.5	166	26.3	0.74 (0.58 to 0.93)	0.01
Breast cancer	6	0.9	19	2.8	0.32 (0.13 to 0.80)	0.02
Colon cancer	4	0.6	13	1.9	0.31 (0.10 to 0.96)	0.04
Stroke (ischemic or hemorrhagic)	28	4.3	13	1.9	2.19 (1.14 to 4.23)	0.02
Coronary heart disease	27	4.1	20	3.0	1.37 (0.77 to 2.45)	0.28
Venous thromboembolism	5	0.8	9	1.3	0.57 (0.19 to 1.69)	0.31

Cummings SR, NEJM 2008

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Tissue Selective Estrogen Complex

- **Breast pain/tenderness was not significantly different between BZA/CE and placebo or raloxifene, but was significantly less than with CE/MPA**

- **There was NOT significant difference in breast density between BZA/CE and placebo**
- **Breast density was significantly increased with CE/MPA compared with placebo**

- **Duration of studies: up to 2 years!**

IMS (2016)

- Epidemiological studies have not found any increased risk of VTE with use of transdermal estrogen.
- The risk of ischemic stroke with MHT may be related solely to oral therapy, with lower doses having a smaller risk and no significant risk occurring with transdermal therapy.

NICE (2015)

- Risk of VTE associated with HRT is greater for oral than transdermal preparation (no greater than baseline population risk)
- Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE
- Taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke

IMS (2016)

- **The risk may be lower with micronized progesterone or dydrogesterone than with a synthetic progestogen for breast cancer.**

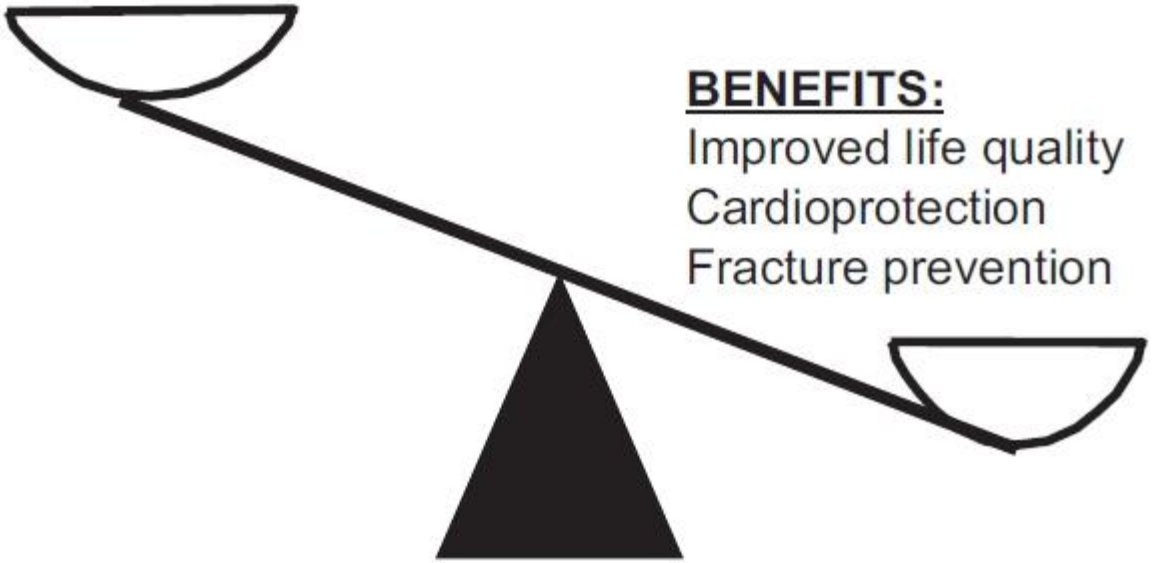
Endocrine Society (2015)

- **For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone for women with a uterus, because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism.**

Transdermal E + micronized P

NO increased risks of:

- Breast cancer
- Stroke
- Thromboembolism
- Gallbladder disease



L'Hermite M, Climacteric 2013

Dose

Use of estrogen: dose

- **Tailoring the dose to a woman's individual needs represents an appropriate strategy in MHT management**

- **Lower MHT doses generally have fewer adverse effects, such as breast tenderness and uterine bleeding**

  - may have a more favorable benefit-risk ratio than standard doses

- **Lower doses of MHT have NOT been tested in long-term trials with clinical outcomes to support an assumed more favorable benefit-risk ratio**

- **Lowest effective dose with upward titration based on clinical response**

NAMS 2012; Endocrine Society 2015; IMS 2016

Use of estrogen: dose

Estrogen doses (mg/day)

Estrogen	Low dose	Medium dose	High dose
Conjugated equine estrogen	≤0.45	0.625	1.25
Piperazine estrone sulfate	≤0.625	1.25, 1.5	2.5
Ethinyl estradiol	<0.01	0.01	>0.01
17β estradiol	≤1	1.5, 2	4
Transdermal 17β estradiol	≤0.25	0.05	0.1
Estradiol valerate	0.5 (1)	1 (2)	2
Esterified estrogens	0.3	0.625	1.25

IMS (2016)

- In the age group 50–60 years or within 10 years after menopause, the benefits of MHT are most likely to outweigh any risk and can be considered as first-line therapy
- Initiation of MHT in the age group 60–70 years requires individually calculated benefit/risk, consideration of other available drugs and the lowest effective dose
- MHT should not be initiated after age 70 years.

NAMS (2014)

- The lowest dose of HT should be used for the shortest duration needed to manage menopausal symptoms.

Duration

Hot flushes in older women

Heart and Estrogen/Progestin Replacement (HERS) study (n=2763)

: Baseline symptoms

	Very frequent	Somewhat frequent
Hot flash	2.8	12.9
Vaginal or genital dryness	10.3	15.4
Vaginal discharge	1.0	4.8
Genital irritation or itching	1.4	8.7
Pelvic cramps	0.6	3.7
Trouble sleeping	12.1	33.8
Early awakening	24.2	28.4
Nausea or vomiting	0.2	3.7
Weight gain	6.9	22.2
Swelling of hands or feet	7.2	27.0
Headaches	2.1	17.2

Data are presented as %.

20%, 70-74 yo
37%, 60-64 yo
47%, 55-59 yo

Avg age: 67 (55-88) & years since menopause: 18 years

Barnabei VM, Obstet Gynecol 2002

Hot flushes in older women

Multiple Outcomes of Raloxifene Evaluation (MORE) trial (n=3167)

: Baseline symptoms

Table 2. Baseline Frequency of Bothersome Hot Flushes by Time Since Menopause

	No. of Participants	Baseline Frequency of Bothersome Hot Flushes, No (%)				
		None of the Time	Little of the Time	Some of the Time	Most of the Time	All of the Time
Years since menopause[a]						
<5	118	37 (31.4)	28 (23.7)	43 (36.4)	6 (5.1)	4 (3.4)
5-9	296	124 (41.9)	112 (37.8)	50 (16.9)	8 (2.7)	2 (0.7)
10-19	1140	796 (70.0)	208 (18.2)	119 (10.4)	13 (1.1)	4 (0.4)
≥20	1601	1269 (79.3)	207 (12.9)	108 (6.7)	13 (0.8)	4 (0.3)
Total	**3167**	2236 (70.6)	556 (17.6)	321 (10.1)	40 (1.3)	14 (0.4)

[a] Data on years since menopause were missing for 12 participants.

Avg age: 67 & years since menopause: 19 years

Huang AJ, Arch Intern Med 2008

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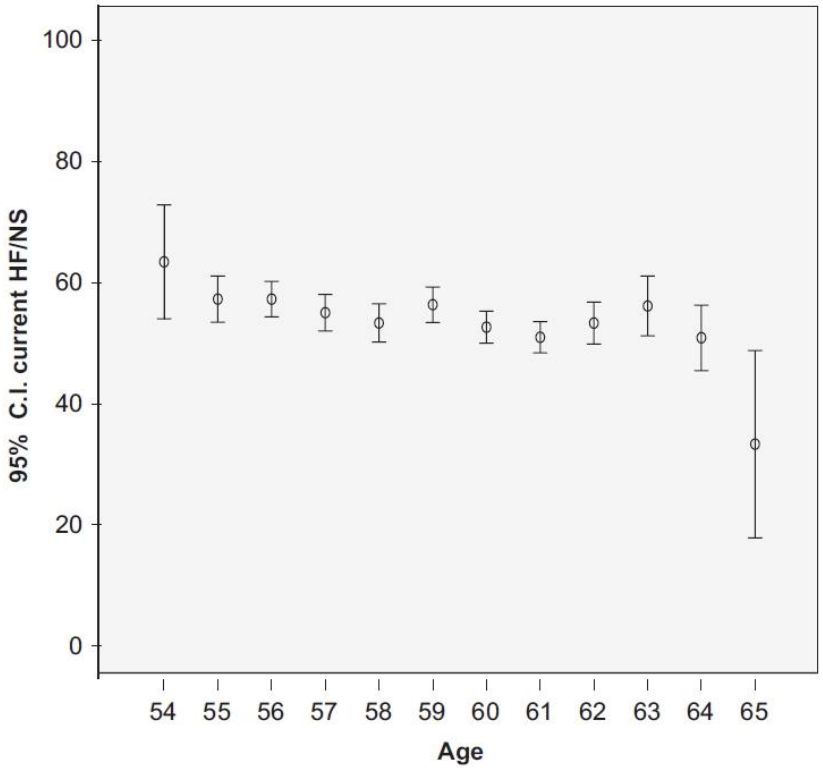
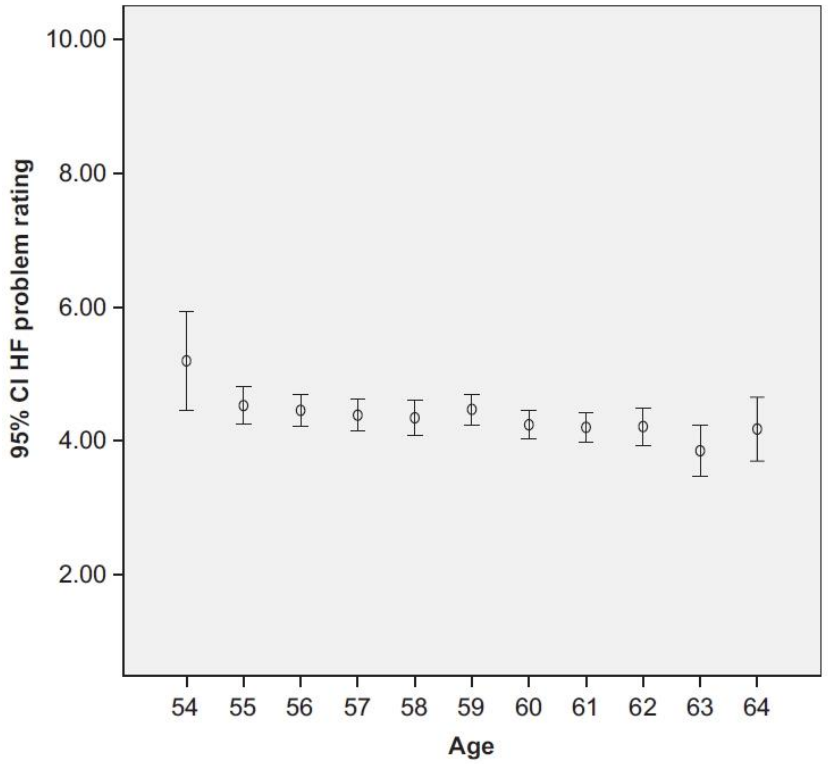
Hot flushes in older women

Cross-sectional cohort study UKCTOCS (n=10418)





Ever had hot flushes (HF): 86%

Median age: 59.75, age at LMP: 49.38, years since LMP: 9.59 years

Hunter MS, BJOG 2012

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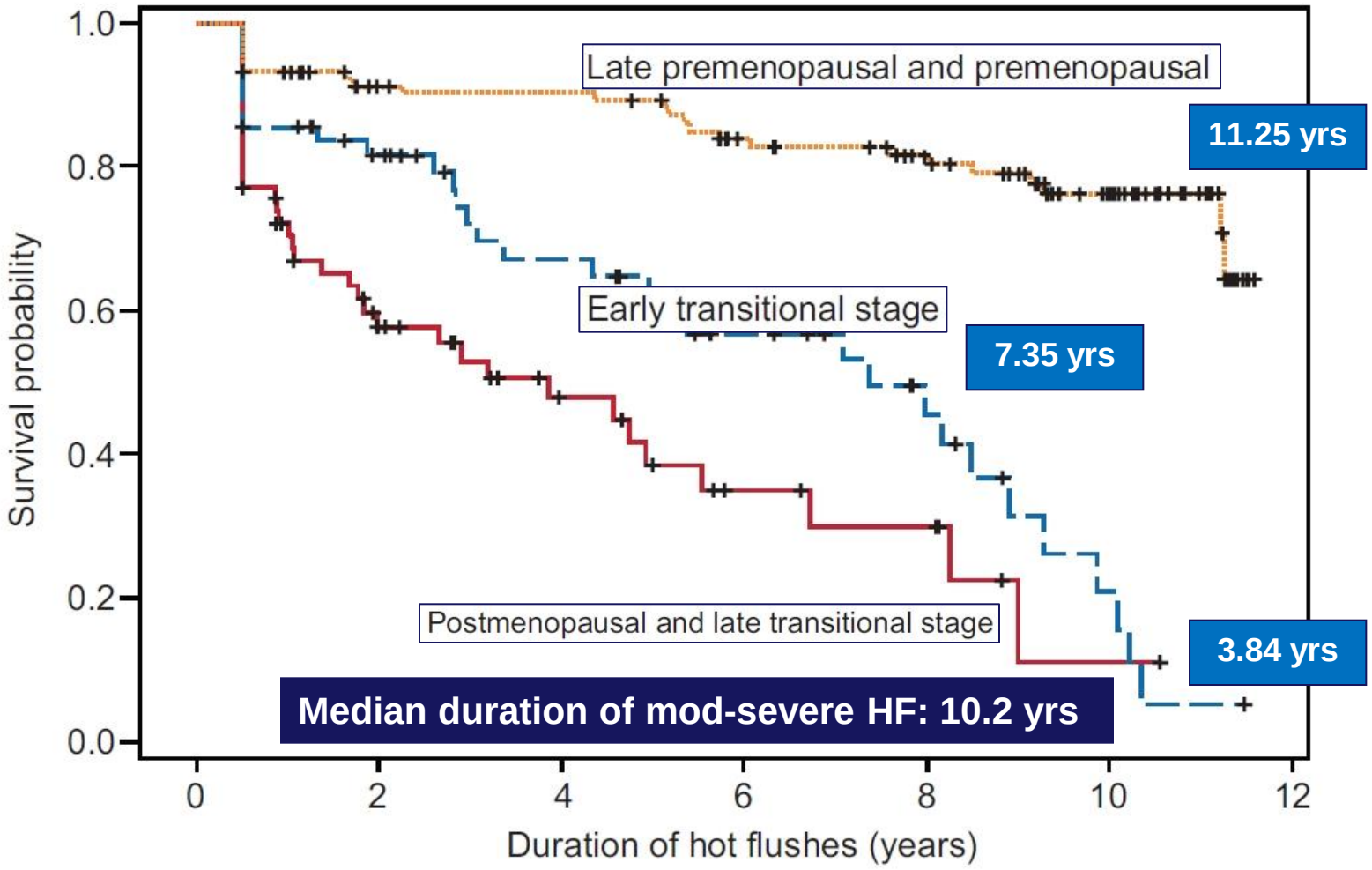
Hot flushes in older women

Penn Ovarian Aging Study (n=349)



Freeman EW, Obstet Gynecol 2011

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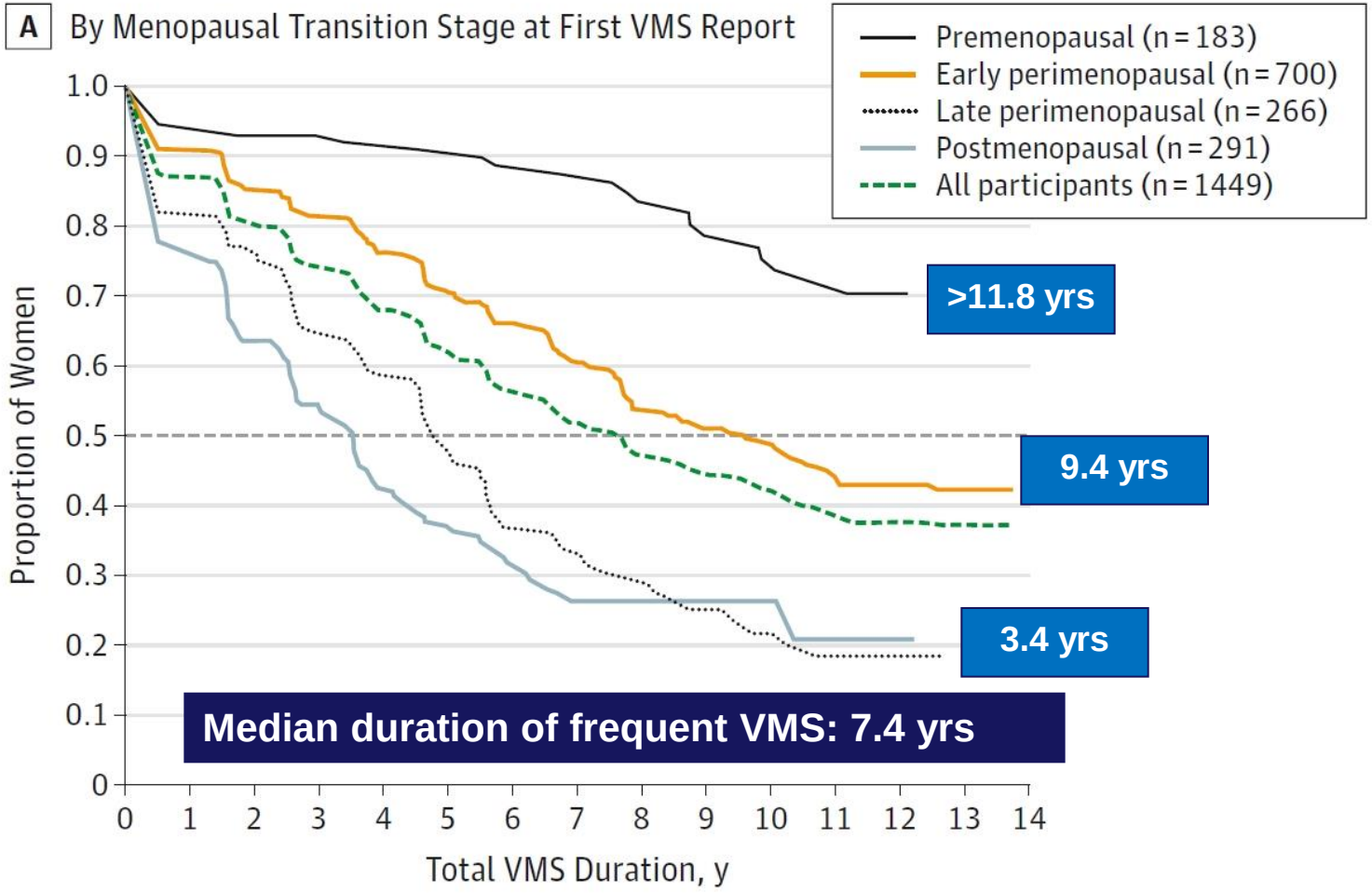
VMS in older women

SWAN study



Avis NE, JAMA Intern Med 2015

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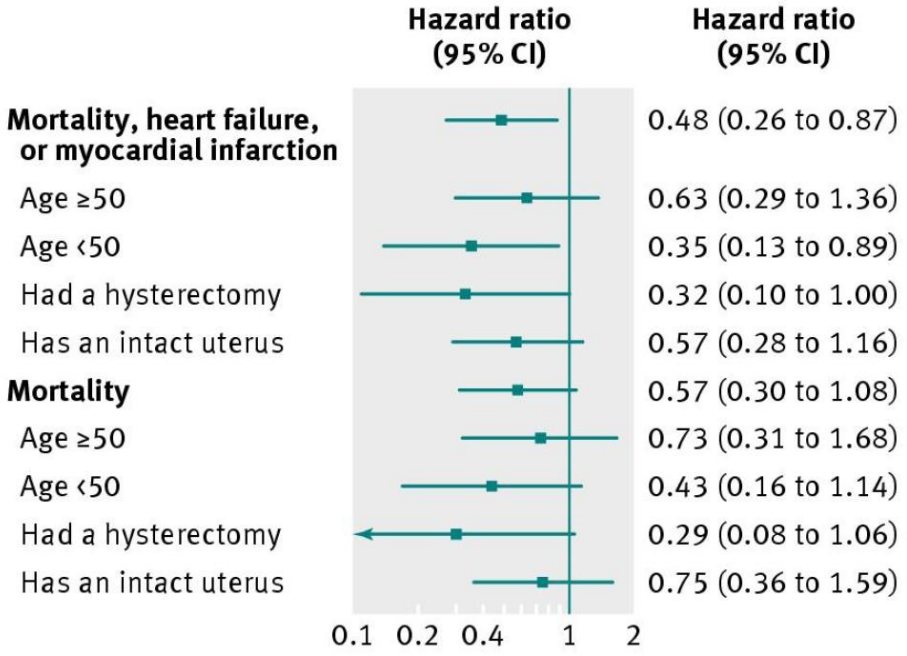
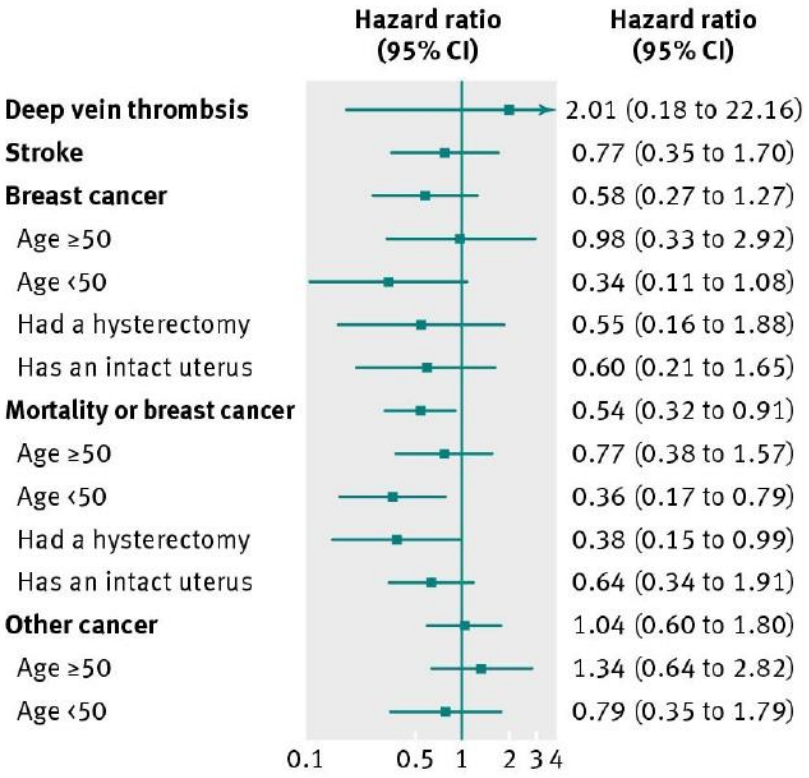
Long-term HT

Danish Osteoporosis Prevention Study (DOPS)





Schierbeck L, BMJ 2012

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IMS (2016)

- There are no reasons to place mandatory limitations on the duration of MHT

NAMS (2015)

- Extending MHT use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinicians has determined that the benefits of menopause symptom relief outweigh the risks.

ACOG (2014)

- The ACOG recommends against routine discontinuation of systemic estrogen at age 65 years.
- The decision to continue MHT should be individualized and be based on a woman's symptoms and the risk–benefit ratio, regardless of age.

Conclusion

- **Non-oral route is recommended for older women or long-term users**
  - **micronized progesterone could be preferred**
- **Lowest effective for the shortest duration**
  - **NO reasons to place mandatory limitations on the duration**
- **INDIVIDUALIZATION based on benefits and risks of each patient**


Thank you for your attention!
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