Progestin-only systemic hormone therapy for menopausal hot flashes

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EDITORIAL

Progestin-only systemic hormone therapy for menopausal hot flashes

Clinicians treating postmenopausal hot flashes often recommend “systemic estrogen treatment.” However, progestin-only therapy also can effectively treat hot flashes and is an option for women with a contraindication to estrogen therapy.

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Hot Flashes

- A sensation of intense heat that can cause sweating and heart palpitation.
- Hypoestrogenemia

01 Symptoms

>73% of postmenopausal women

Sensation of extreme heat

Decreased cognitive function

Shivering

Fatigue

Sleep disturbances

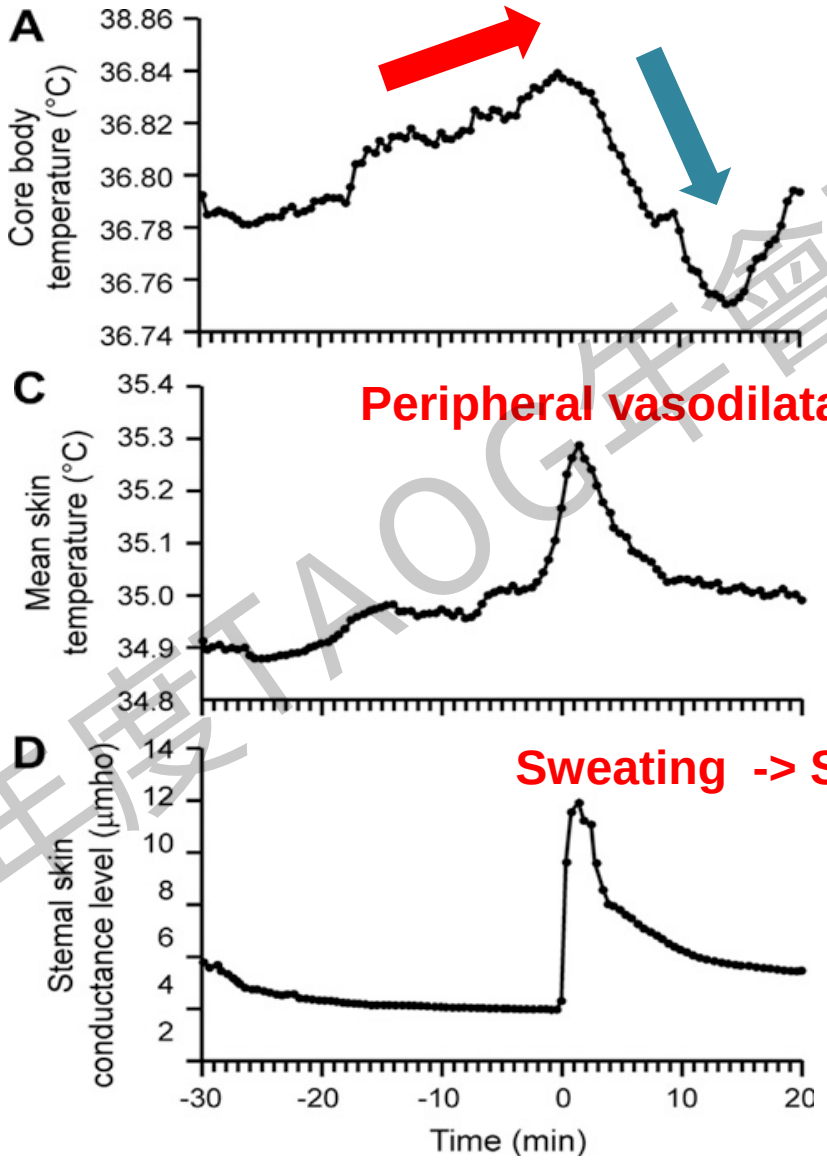
Anxiety/ Depression

Up to 30 times a day
May persist for 7 years
Decreased quality of life
Increased use of medical resources

J Womens Health (Larchmt). 2013 Nov;22(11):983-90.
Lancet. 2017 May 6;389(10081):1775-1777.

Signs

A small increase in core temperature before a hot flush

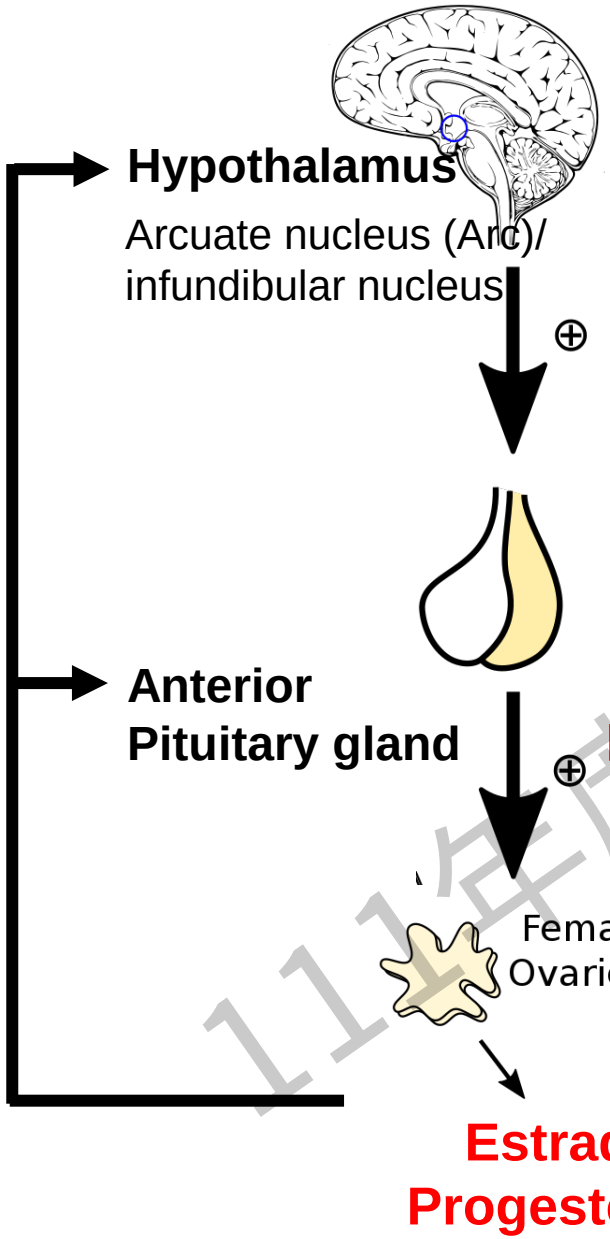


Peripheral vasodilatation → skin reddening

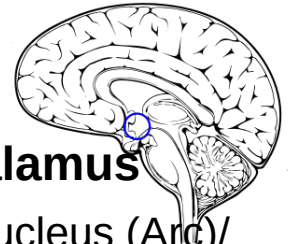
Sweating -> Shivering

Front Neuroendocrinol. 2013 Aug; 34(3)

01 Pathophysiology



01 Pathophysiology



Hypothalamus

Arcuate nucleus (Arc)/
infundibular nucleus

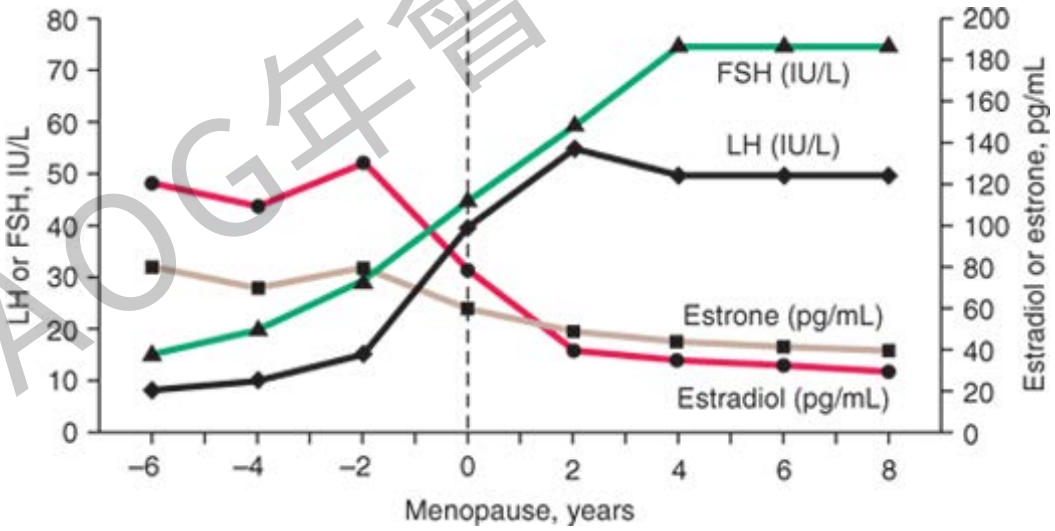
⊕ **GnRH**

Anterior Pituitary gland

⊕ **FSH**
LH

Female
Ovaries

Estradiol
Progesterone



Harrison's Endocrinology, 4e, CH 16

Current treatment options for hot flush

- Hormone replacement therapy
- Anti-seizure medication (Carbapentin)
- Anti-depressants : Selective serotonin receptor inhibitor (SSRI)
- Neurokinin receptor antagonists
- Other alternatives : Dietary isoflavones (soy), yoga, mindfulness, acupuncture, Chinese herbal medicine, aerobic exercise

Drug	Evidence of effectiveness	Adverse effects
Paroxetine (SSRI)	• Low dose (7.5mg/d): Significant improvement at **4 weeks** [RCT, placebo controlled, n=591] (Menopause. 2013 Oct;20(10):1027-35.) • Approved by FDA for hot flashes	• Nausea, fatigue, dizziness • **Inhibitor of CYP2D6** →decreased the active metabolite of tamoxifen
Gabapentin	• High dose (900mg/d): Significant improvement at **4 weeks** [RCT,placebo-controlled, n=420] Lancet. 2005 Sep 3; 366(9488): 818–824.	• Dizziness
Alternative treatments: **Dietary isoflavones (soy), yoga, mindfulness, acupuncture**, Chinese herbal medicine, aerobic exercise		

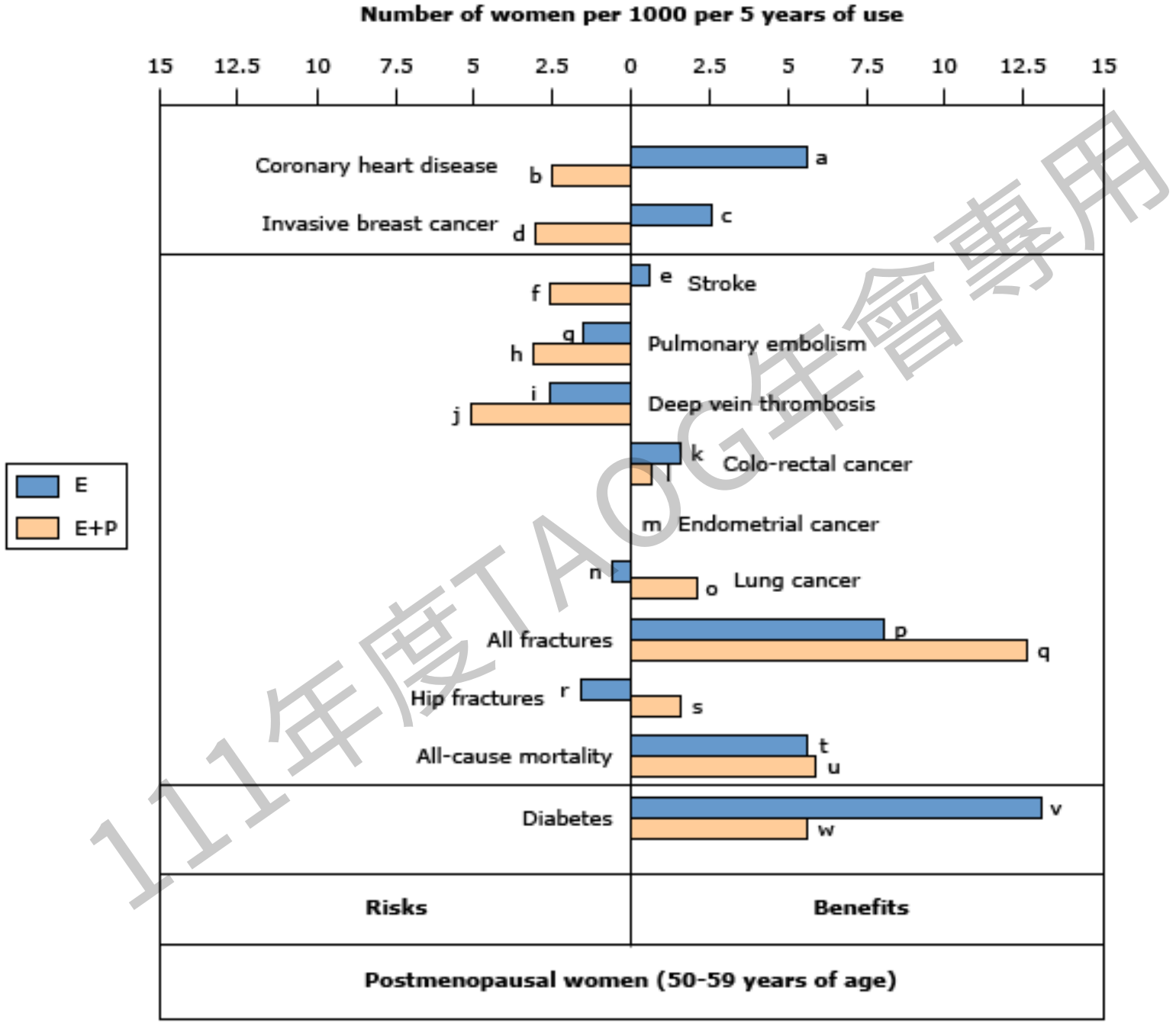
- **Improvement of hot flashes in placebo group?**
- **Often small sample size**
- **Mechanism unclear**
- **Benefit not clinically meaningful**
  - Gabapentin : decrease 0.9 to 1.7 episodes per day

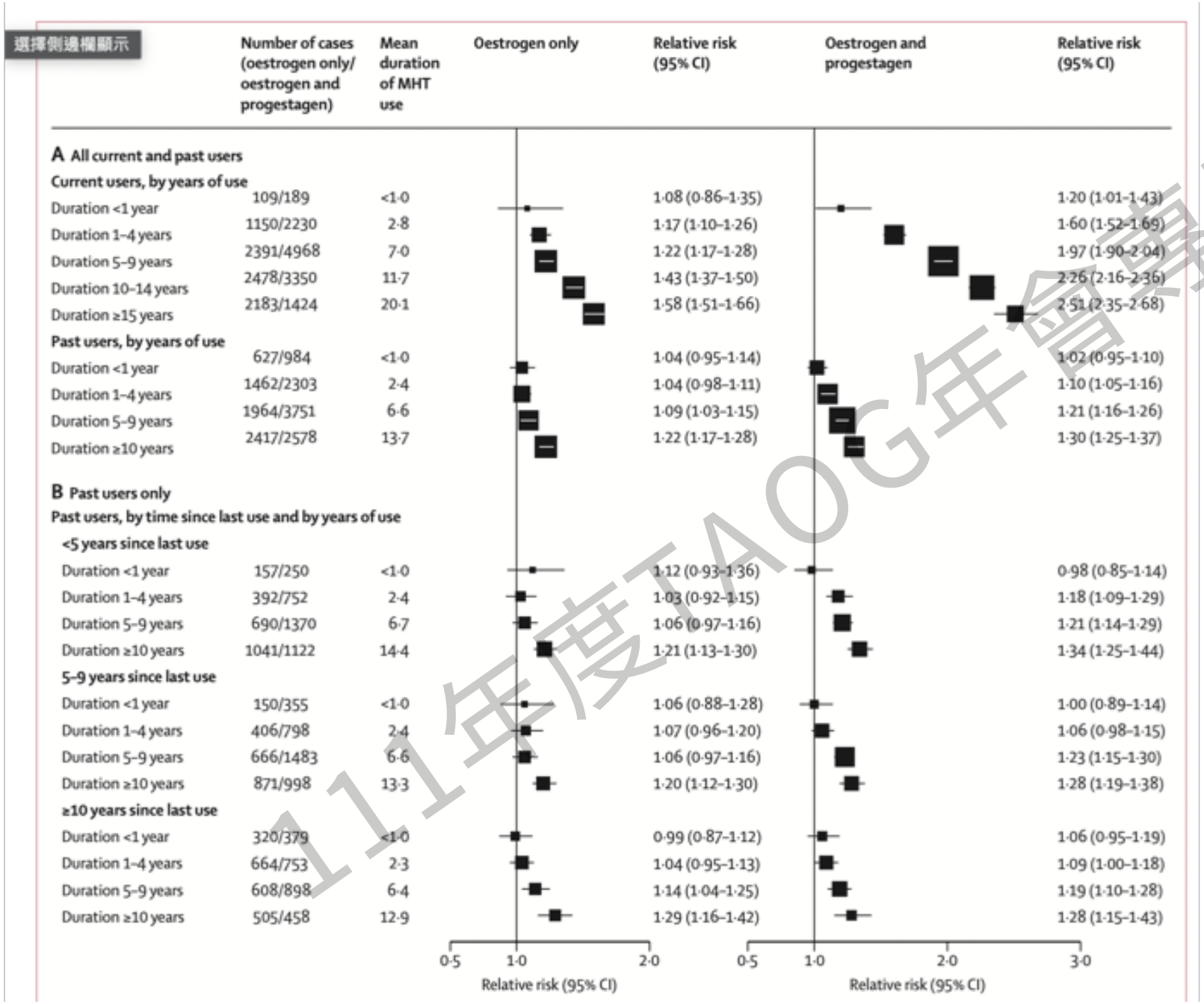
Am J Psychiatry. 2008 Oct; 165(10):1251-5.
J Clin Oncol. 2009 Jun 10;27(17):2831-7.
Clin Ther. 2018 Oct;40(10):1778-1786

Hormone replacement therapy (HRT)

Outcomes	No. of patients(Annualized %) Estrogen + Progestin (n=8506)	Placebo (n=8102)	Hazard ratio	Nominal 95% CI
Fractures(total)	650(1.47)	788(1.91)	**0.76**	**0.69-0.85**
Endometrial cancer	22(0.05)	25(0.06)	0.83	0.47-1.47
Death (total)	231(0.52)	218(0.53)	0.98	0.82-1.18
Coronary heart disease	163(0.37)	122(0.30)	**1.29**	**1.02~1.63**
Invasive breast cancer	166(0.38)	124(0.30)	**1.26**	**1.00-1.59**

JAMA. 2002 Jul 17;288(3):321-33.





HRT increase the risk of breast cancer-meta-analysis of worldwide epidemiologic evidences

Collaborative Group on hormone factors in Breast cancer. Lancet 2019; 394:1159-68

Increase risk of thromboembolism with HRT

TABLE 3. Effects of HRT on Risk for VTE by Factor V Leiden Genotype

Genotype	Treatment	Cases (n=48)	Controls (n=112)	OR*	95% CI	*P*	Adjusted OR†	Adjusted 95% CI	Adjusted *P*
Wild-type	Placebo	8	45	1.0	...	...	1.0	...	...
	HRT	32	60	3.7	1.4–9.4	<0.01	4.5	1.2–16.9	0.02
Leiden	Placebo	2	4	1.0	...	...	1.0	...	...
	HRT	6	3	5.7	0.6–53.9	0.13	10.2	0.3–344	0.20

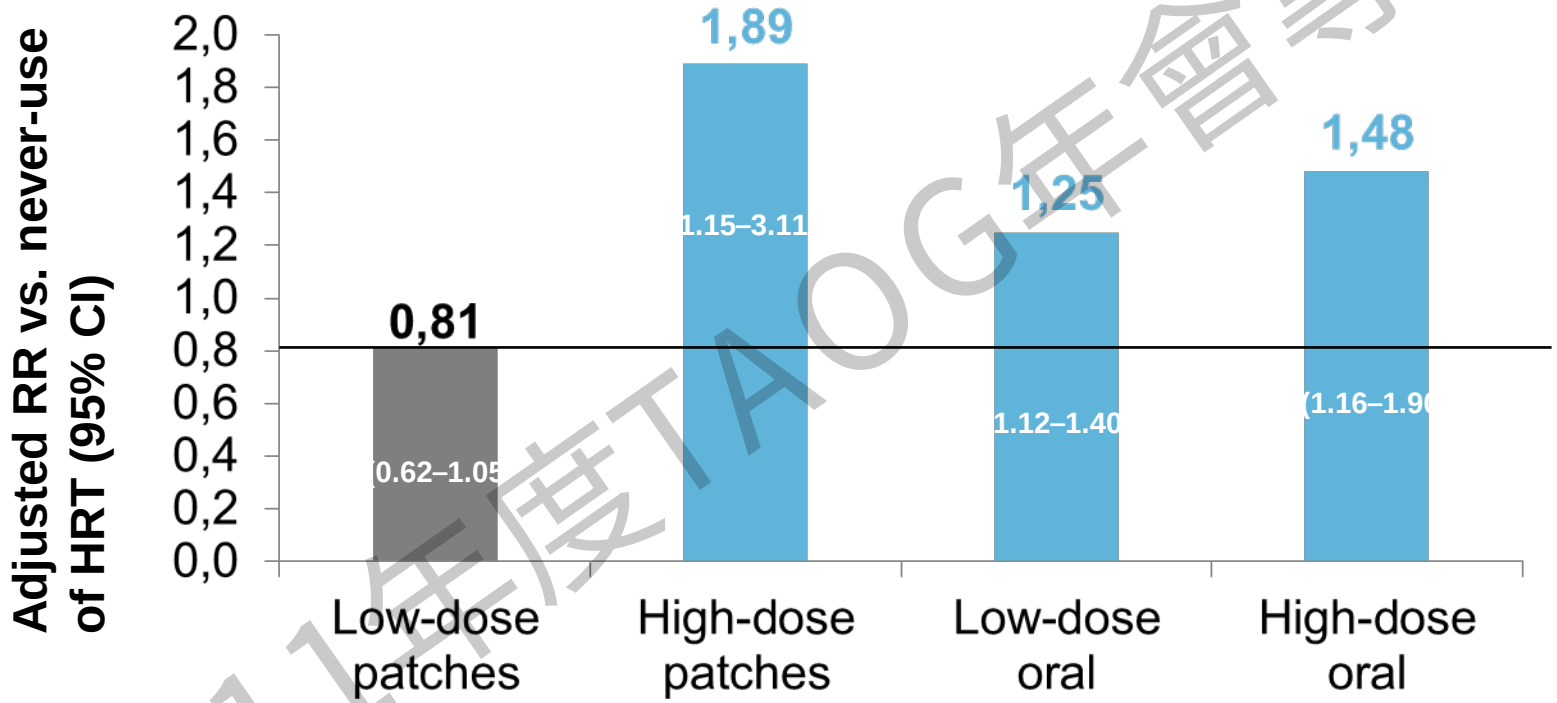
*Based on conditional logistic regression taking into account age- and clinic-matched case-control design and adjusting for treatment assignment (HRT versus placebo).

†Also adjusted for a history of MI and recent hospitalization.

Herrington et al., Artherioscler Thromb Vasc Biol. 2002; 22:1012-17

Risk of Stroke Associated with Route of Administration

- Case-control study from the UK General Practice Research Database (n=75,668 and stroke cases, n=15,710)



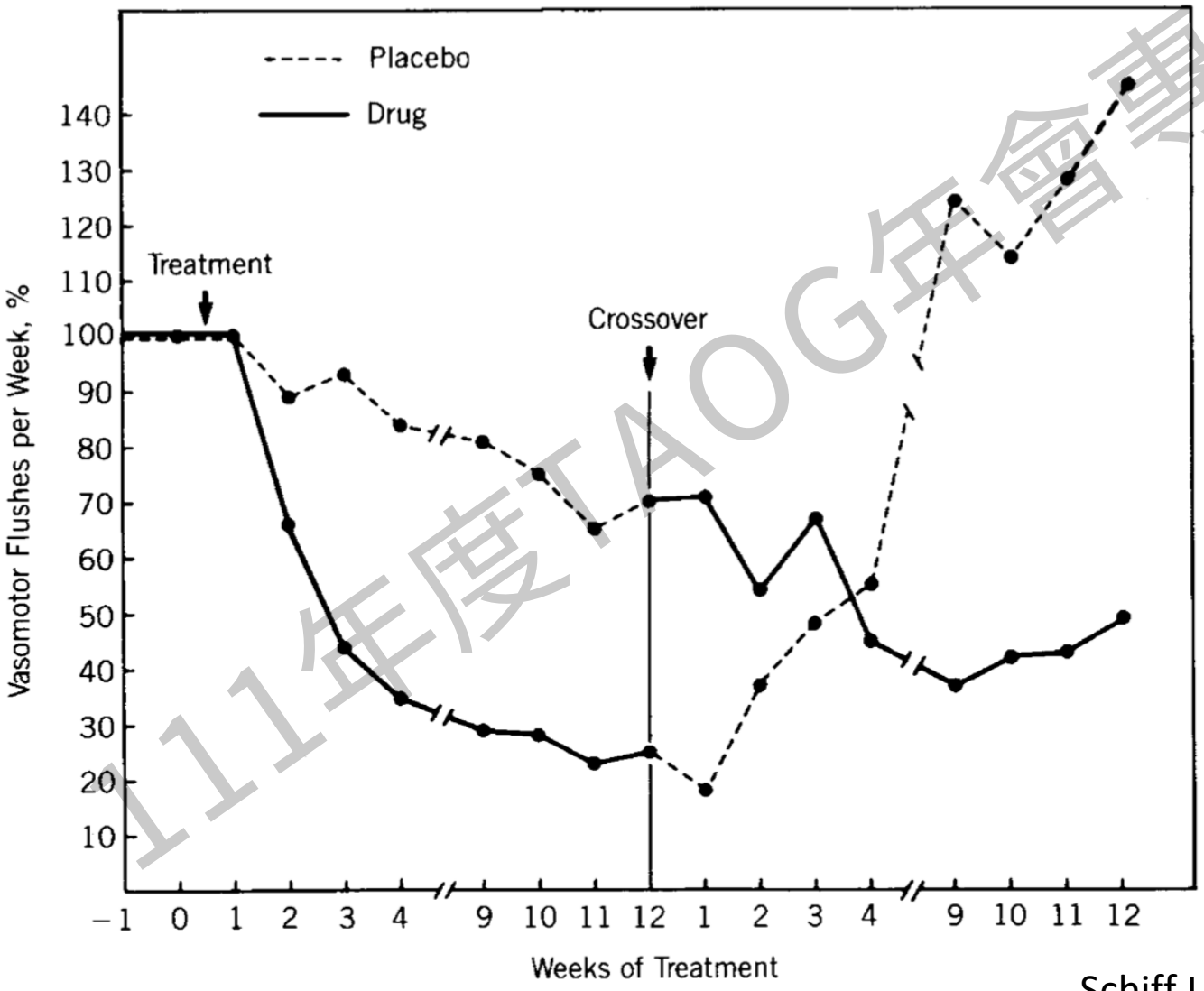
- **Low-dose transdermal HRT did not appear to increase stroke risk**

Low-dose patch <50ug E, High-dose patch >50ug E; Low-dose oral <0.625 EE or <2mg E; High-dose oral >0.625 EE or >2mg E

Renoux C et al. BMJ 2010;340:c2519.

Monotherapy with progesterone to treat women with contraindications to estrogen

A double-blind crossover study to compare MPA and placebo for hot flushes



Schiff I et al., JAMA. 1980; 244: 1443-1445

Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1 year randomized double-blind trial following premenopausal oophorectomy

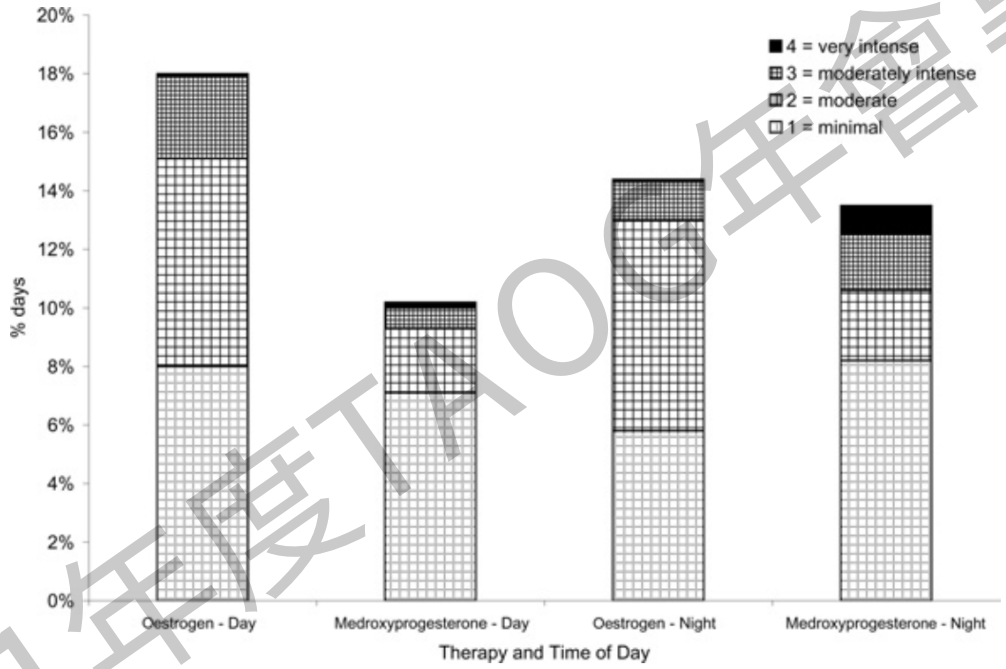


Figure 4 **Percentage of days with each intensity level of vasomotor symptoms over 1 year for both daytime and night-time hot flushes and night sweats during the therapies following premenopausal ovariectomy**

Increasing intensities of hot flushes and night sweats (range 0–4) are shown by the increased density of hatching, and the height of the bars reflects the proportion of days/nights with any vasomotor symptoms.

Prior JC et al., Clinical Science 2007, 112:517-25

Risk of Thromboembolism Associated with Different Progestogens

ESTHER case-control study

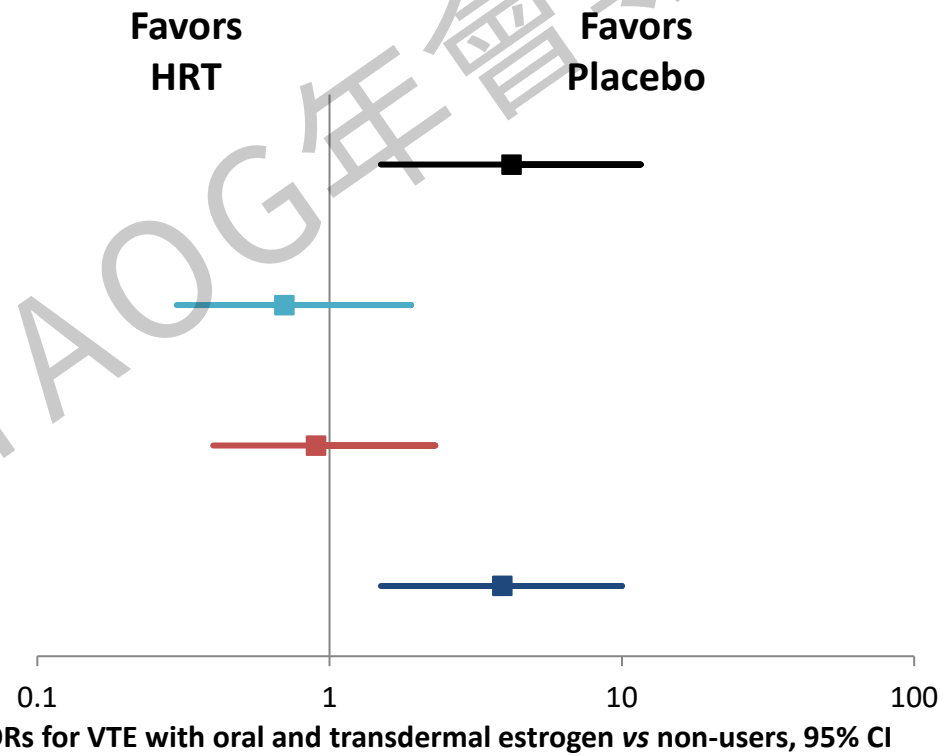
271 consecutive VTE cases (mean age: 61.6 years) and 610 controls (mean age: 61.5 years)

Oral estrogen: 4.2 (1.5, 11.6)

Micronized progesterone: 0.7 (0.3, 1.9)

Pregnane derivatives: 0.9 (0.4, 2.3)
e.g. Dydrogesterone

Norpregnane derivatives: 3.9 (1.5, 10.0)
e.g. Nomegestrol acetate

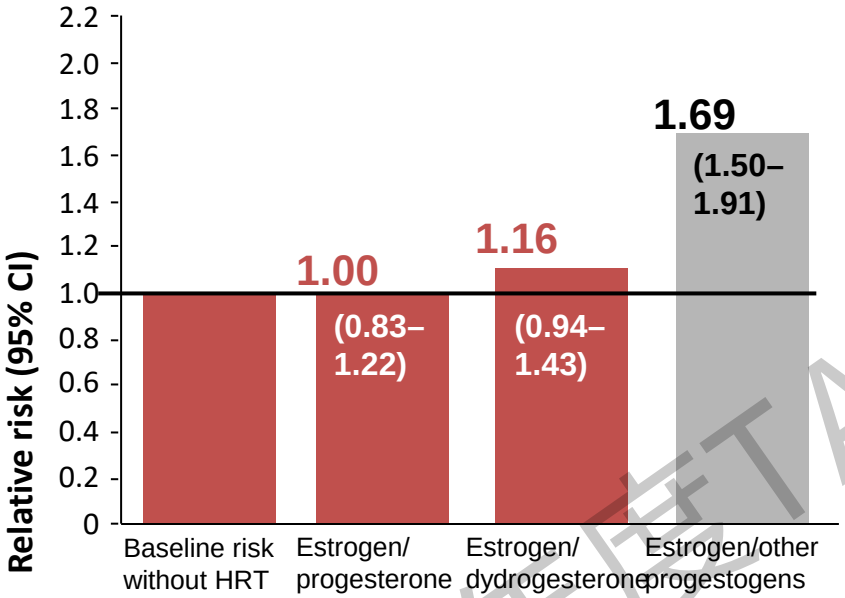


➔ Micronized progesterone and pregnane derivatives appear to have an acceptable thrombotic risk profile

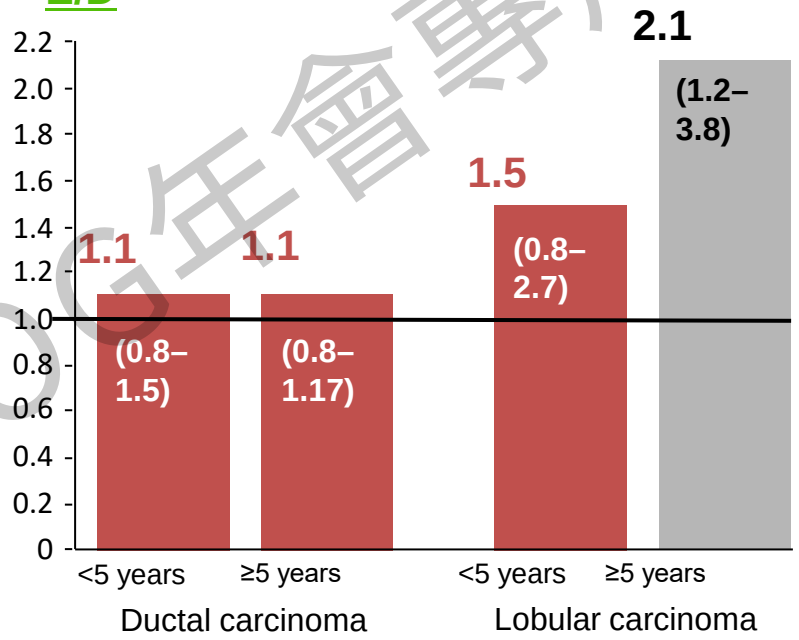
Canonico M. *Circulation* 2007;115:840–845

Choice of Progestogen and Breast Cancer Risk: E3N French Cohort Study

Risk of all breast cancer



Risk of breast cancer subtypes with E/D



Not statistically significantly different from risk without HRT

Significantly different from the risk without HRT (for all breast cancer p<0.001; for subtypes p=0.05)

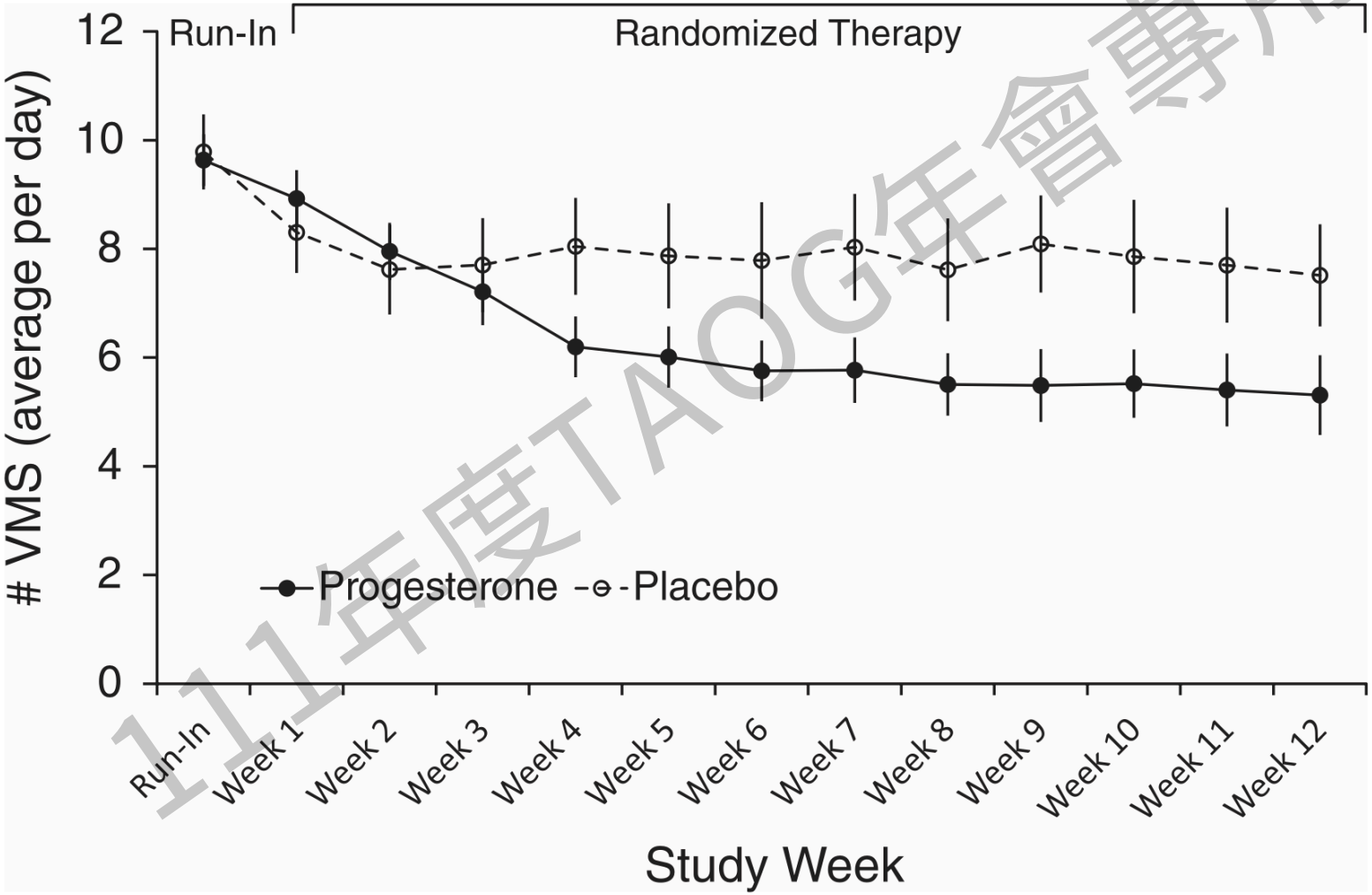
N = 80,377 women, for an average treatment duration of 8.1 years

Overall 77.7% were ductal breast cancers vs. 22.3% lobular breast cancers

Risk elevation may not be uniform for all progestogens

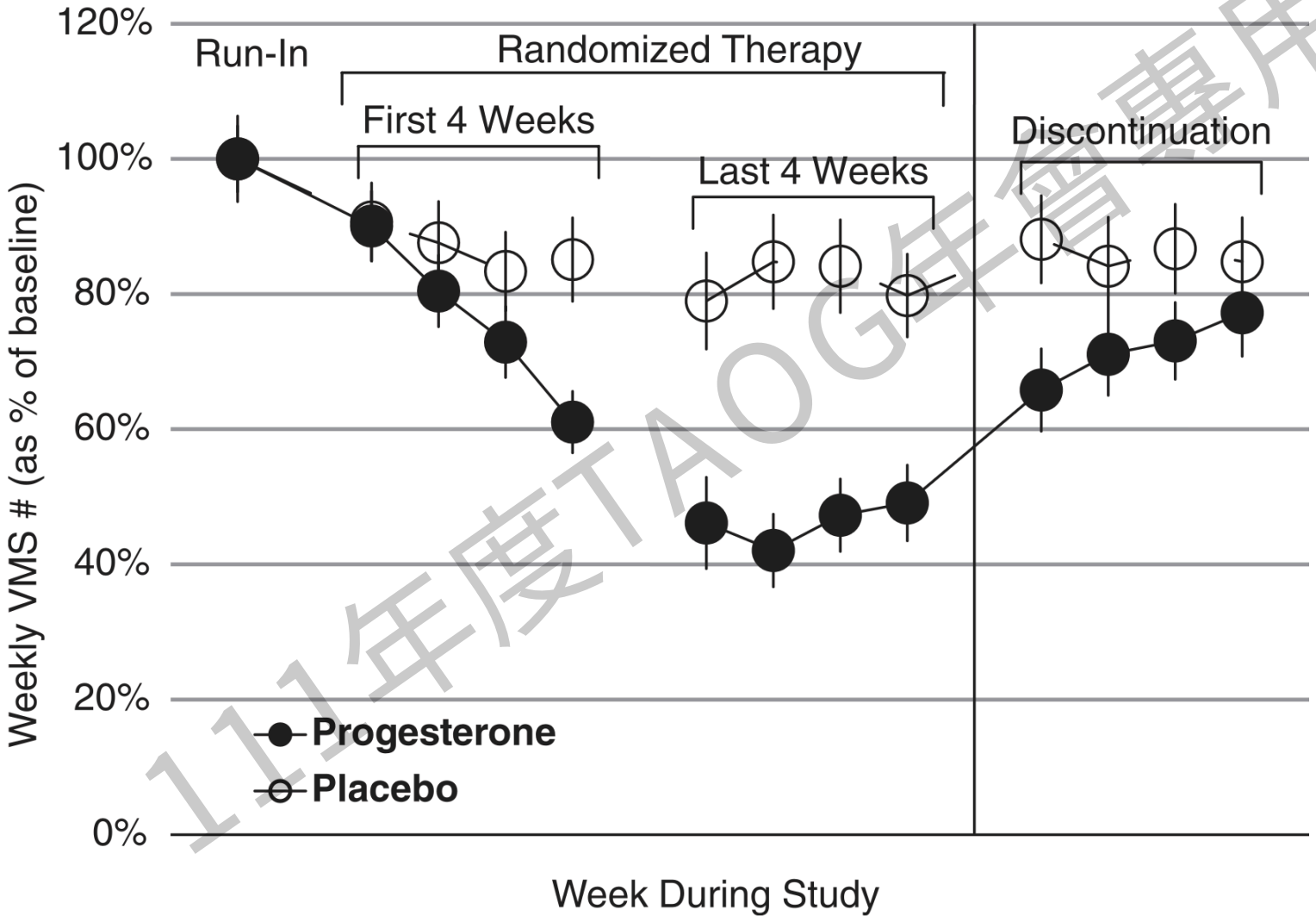
Fournier A et al. Breast Cancer Res Treat 2008;107:103–11;
Fournier A et al. J Clin Oncol. 2008 ;26:1260–1268.

Micronized progesterone for hot flush and night sweating treatment



Prior JC et al., Gynecological Endocrinology, 2012; 28(S2)7-11

Micronized progesterone for VMS and withdrawal rebound



Prior JC et al., Gynecological Endocrinology, 2012; 28(S2)7-11

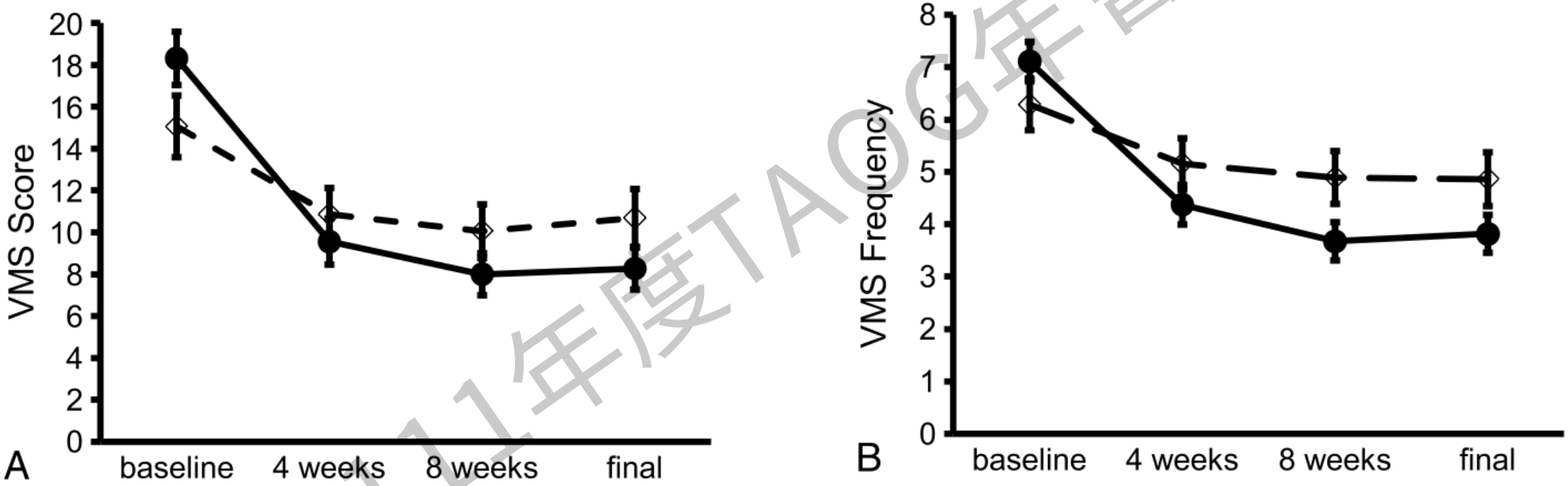
Micronized progesterone for VMS: A placebo-control RCT in early postmenopausal women

TABLE 2. *Hot flush and night sweat (VMS) score, frequency, and severity by therapy assignment*

	Progesterone (n = 68), mean (95% CI)	Placebo (n = 46), mean (95% CI)	Difference, mean (95% CI)
VMS score[a] per day			
Run-in	18.3 (15.8 to 20.8)	15.1 (12.1 to 18.0)	3.2 (−0.6 to 7.1)
Change from run-in (adjusted mean difference)			
Week 4	**−8.7 (−10.9 to −6.6)**	**−3.8 (−5.7 to −1.8)**	**−3.4 (−5.6 to −1.1)**
Week 8	**−10.3 (−12.2 to −8.4)**	**−4.6 (−6.9 to −2.3)**	**−4.1 (−6.4 to −1.8)**
Final 4 wk	**−10.0 (−12.0 to −8.1)**	**−4.4 (−6.6 to −2.2)**	**−4.3 (−6.6 to −1.9)**
VMS frequency per day			
Run-in	7.1 (6.4 to 7.9)	6.3 (5.3 to 7.3)	0.8 (−0.4 to 2.0)
Change from run-in (adjusted mean difference)			
Week 4	**−2.7 (−3.3 to −2.1)**	**−1.1 (−1.8 to −0.5)**	**−1.4 (−2.2 to −0.6)**
Week 8	**−3.4 (−4.0 to −2.9)**	**−1.4 (−2.1 to −0.7)**	**−1.8 (−2.6 to −1.0)**
Final 4 wk	**−3.3 (−3.9 to −2.7)**	**−1.4 (−2.1 to −0.8)**	**−1.6 (−2.4 to −0.8)**
VMS severity (1-4) per day			
Run-in	2.6 (2.5 to 2.8)	2.4 (2.2 to 2.6)	**0.2 (0.0 to 0.5)**
Change from run-in (adjusted mean difference)			
Week 4	**−0.6 (−0.7 to −0.4)**	**−0.3 (−0.4 to −0.1)**	**−0.2 (−0.5 to −0.0)**
Week 8	**−0.6 (−0.8 to −0.5)**	**−0.4 (−0.6 to −0.2)**	−0.2 (−0.4 to 0.1)
Final 4 wk	**−0.6 (−0.8 to −0.5)**	**−0.4 (−0.5 to −0.2)**	**−0.2 (−0.4 to −0.0)**

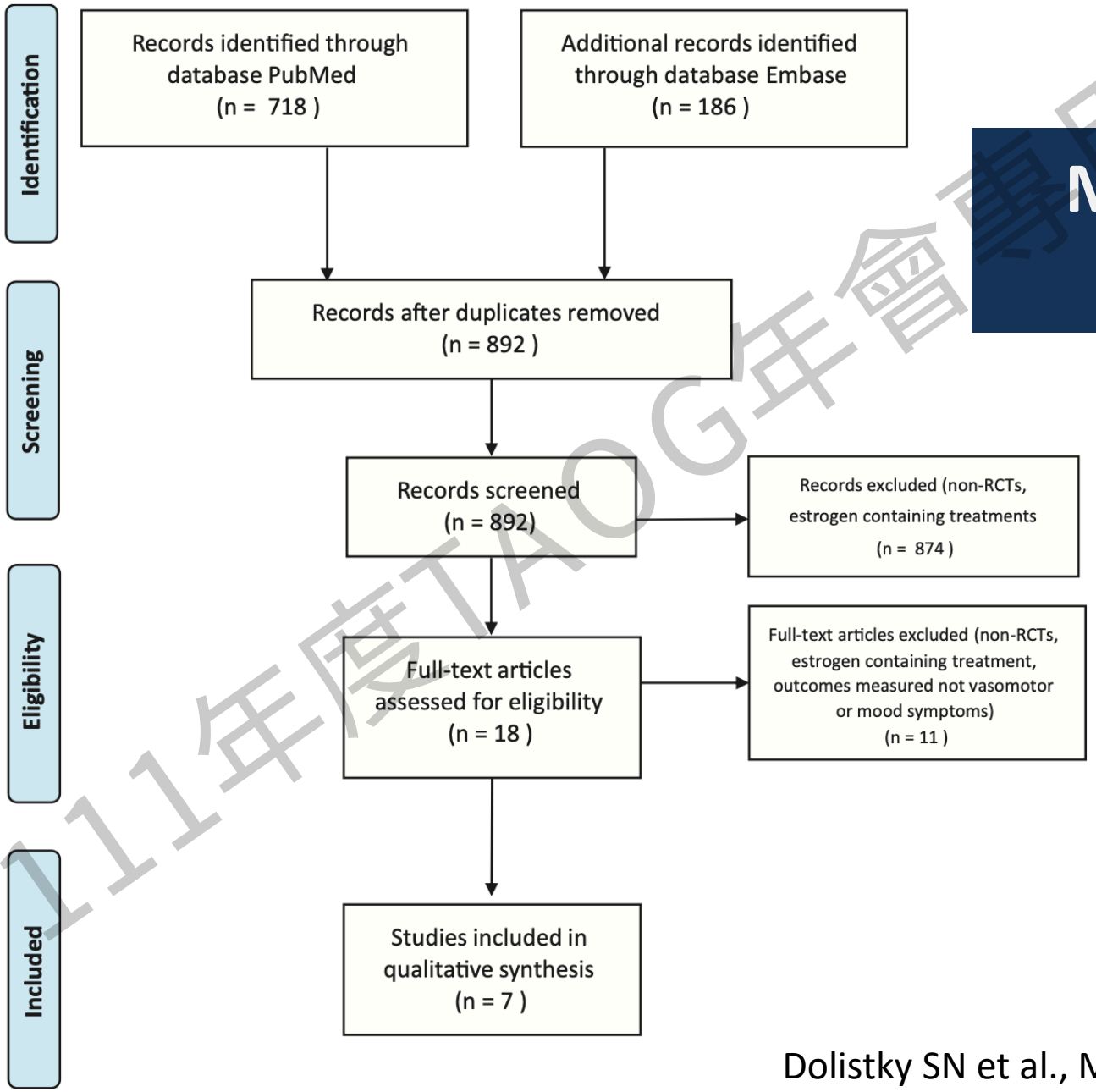
Hitchcock CL et al., Menopause 2012, 19(8):886-893

Micronized progesterone for VMS: A placebo-control RCT in early postmenopausal women



Hitchcock CL et al., Menopause 2012, 19(8):886-893

Meta-analysis of RCTs

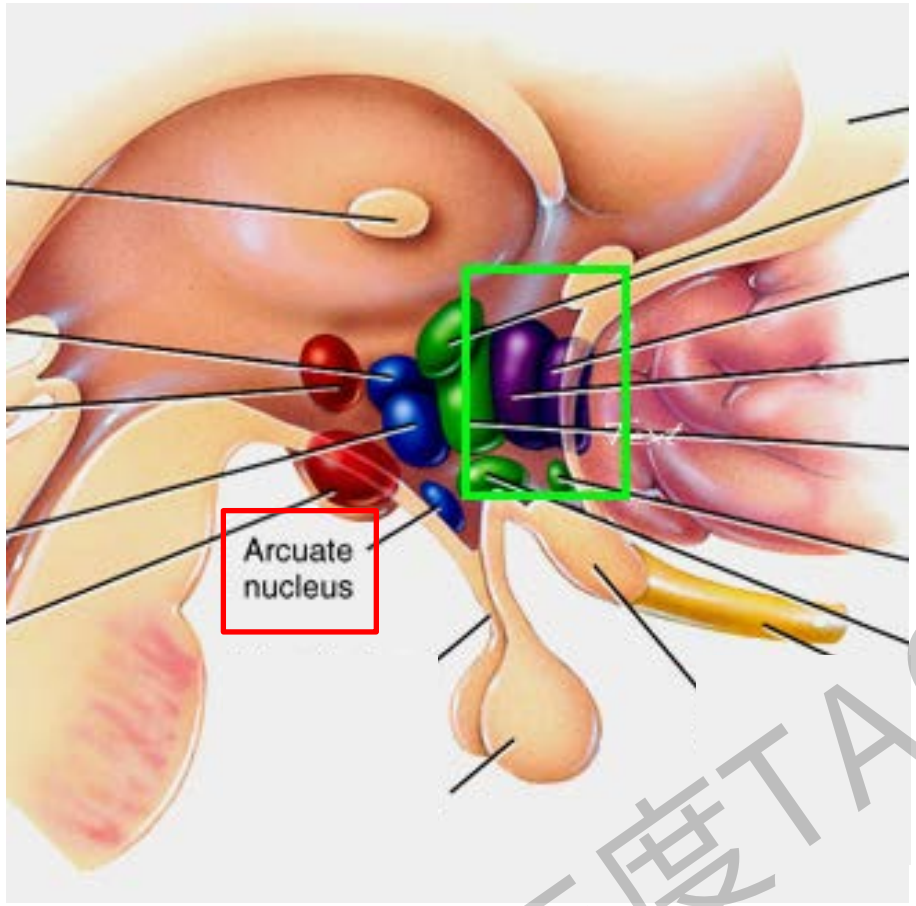


Dolistky SN et al., Menopause 2020, 28(2):217-224

Optimal route and dosage of progestin monotherapy

- Transdermal progesterone 3-6 months
  - No effect on VMS from 5-60 mg
- Oral medroxyprogesterone
  - 20 mg is effective in VMS, whereas 10 mg has not response
- 300 mg micronized progesterone
  - Improve in VMS
- The most common reason for discontinuation is vaginal bleeding and headache
- All trials showed no improvement in mood symptoms

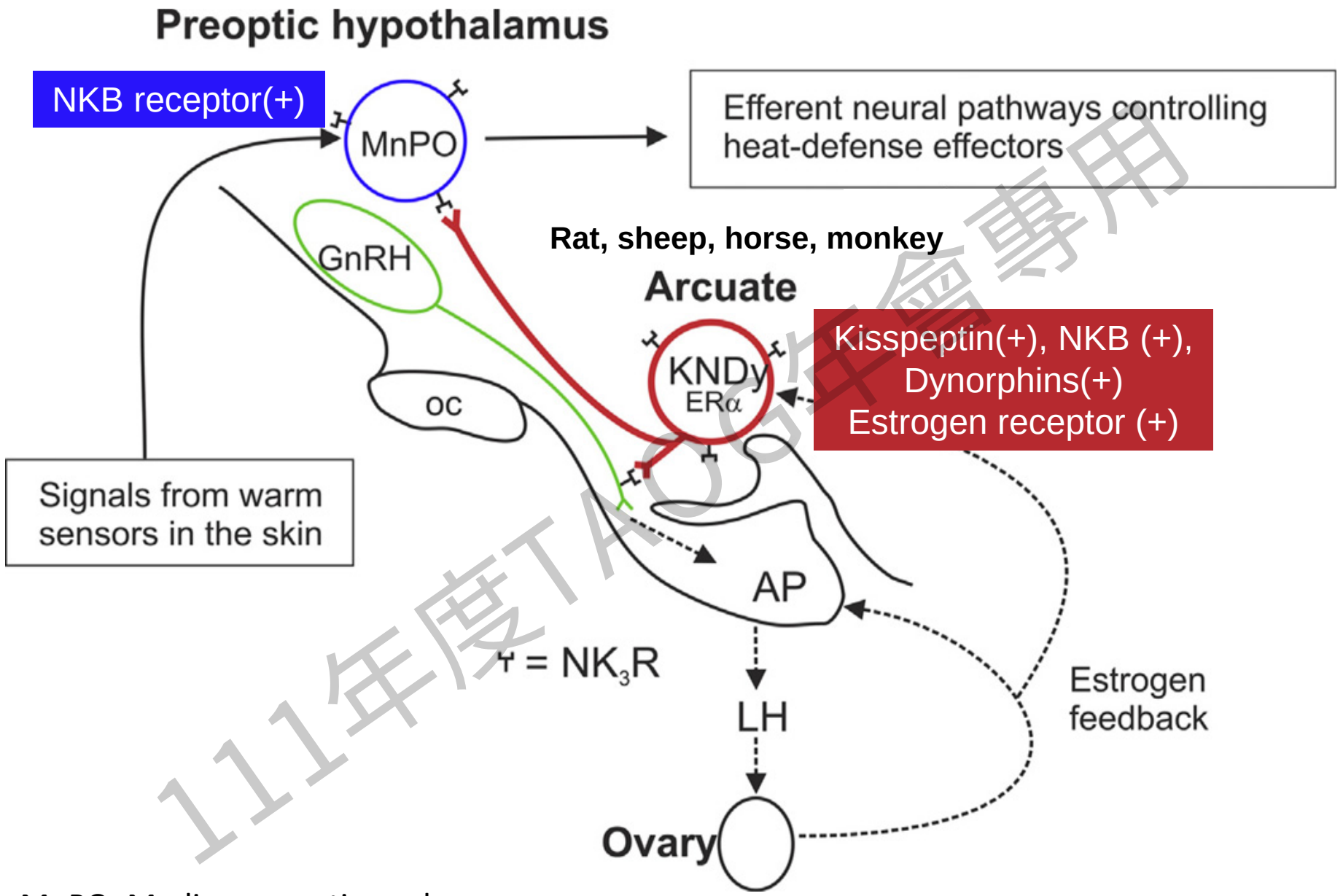
Dolistky SN et al., Menopause 2020, 28(2):217-224



Median preoptic area(mPOA)

Arccuate nucleus(Arc)

Kisspeptin-expressing neurons, coexpress Neurokinin B(NKB)



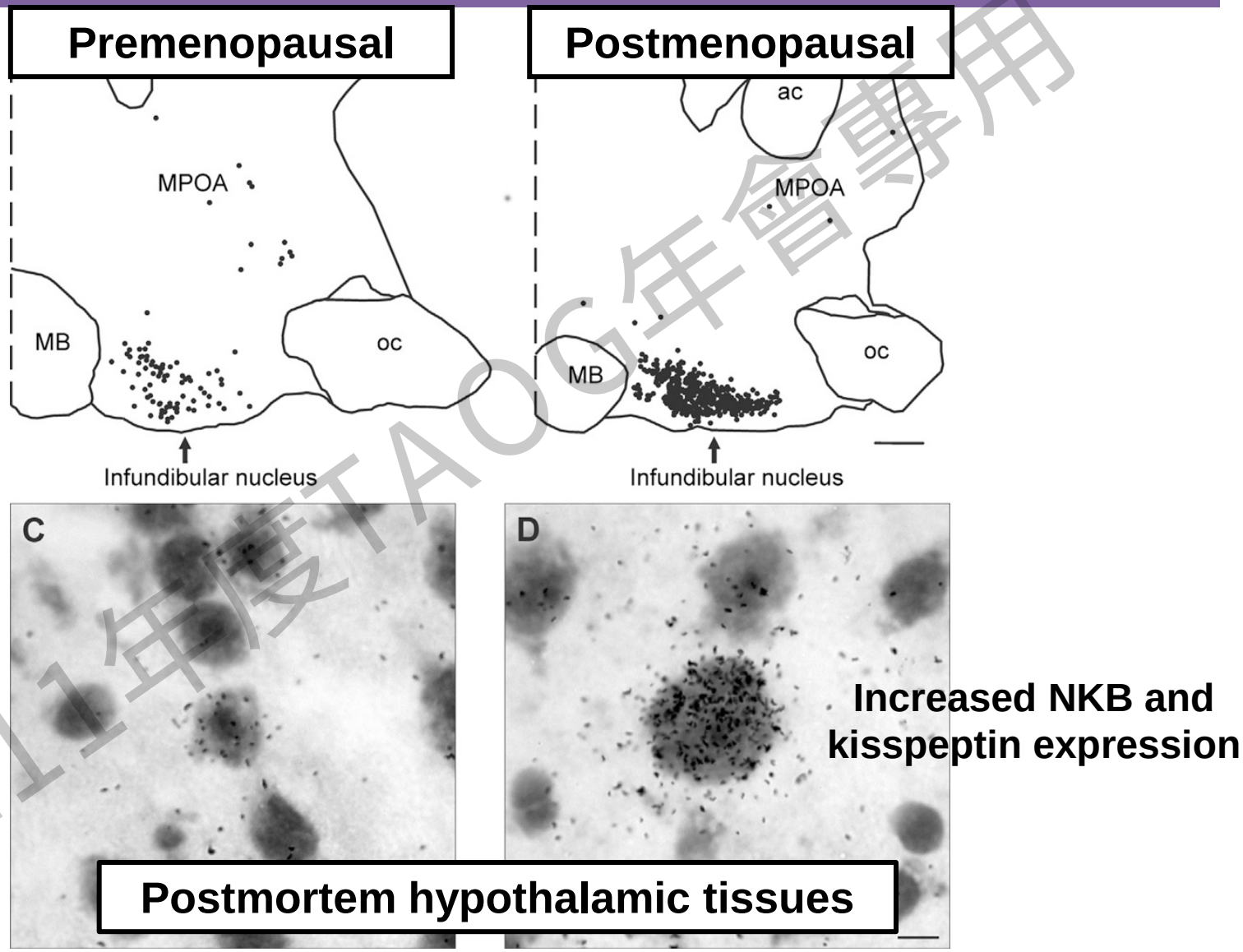
MnPO: Median preoptic nucleus
AP: Anterior pituitary

Front Neuroendocrinol. 2013 Aug; 34(3)

Hypertrophy of infundibular neurons: KNDy neurons

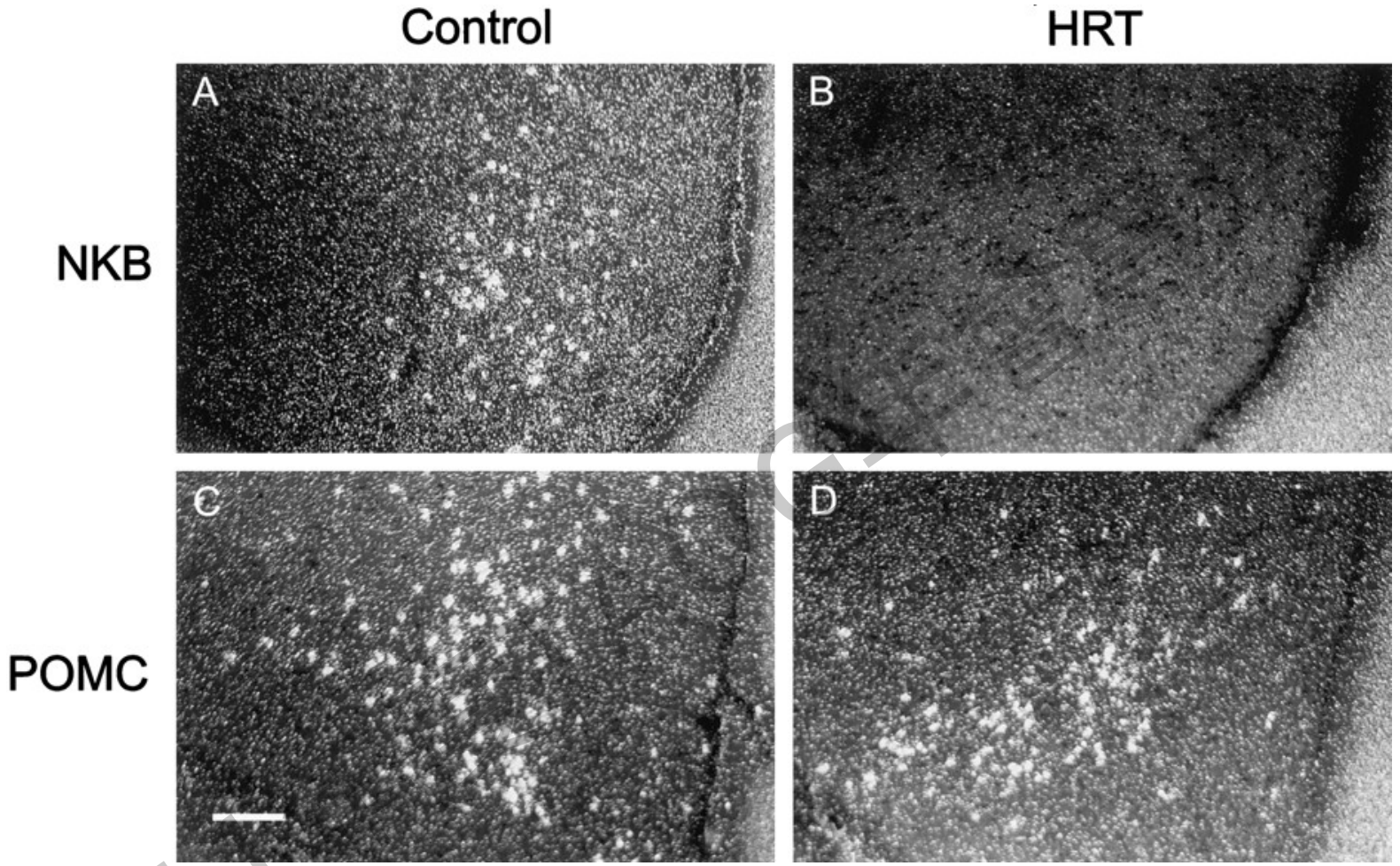
Estrogen receptor (+), kisspeptin(+), Neurokinin B (NKB) (+), Dynorphins(+)

The **only** site with coexpression of kisspeptin and NKB



Increased NKB and kisspeptin expression

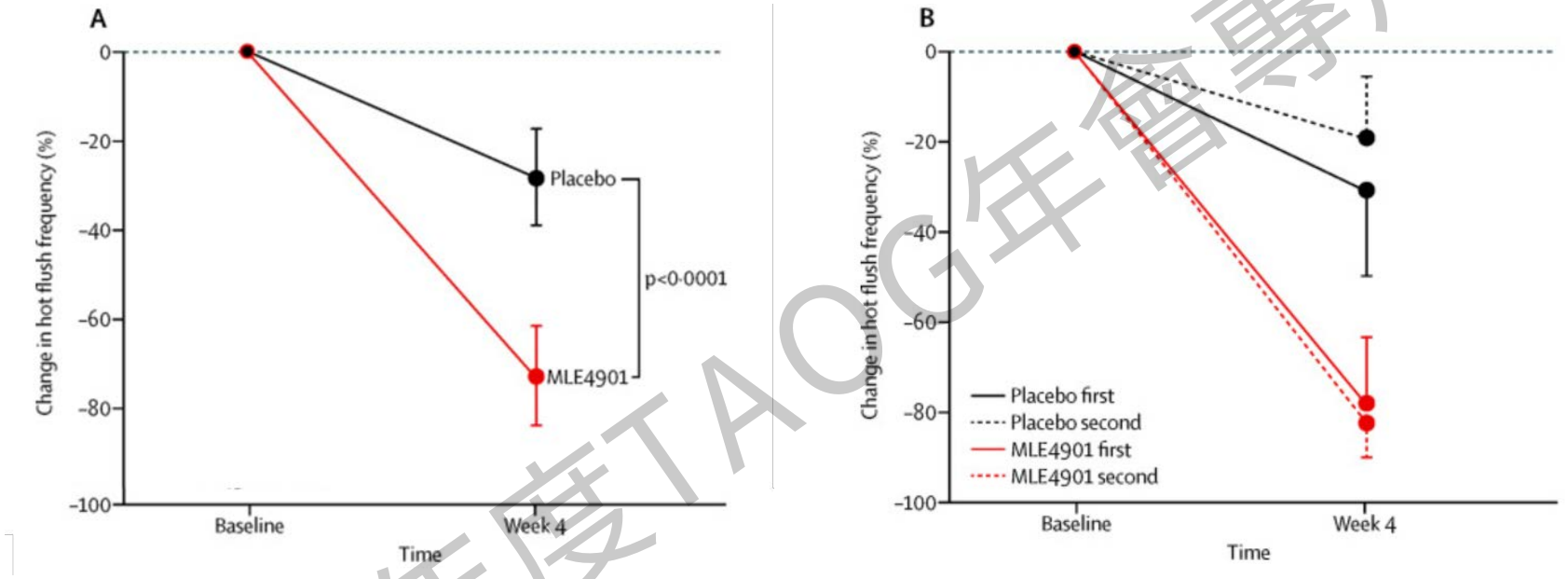
Postmortem hypothalamic tissues



Hormone replacement therapy (HRT) resulted in a striking **reduction** in the number of neurons expressing **NKB mRNA** in the primate infundibular nucleus.

J Clin Endocrinol Metab. 1999 Jun;84(6):2111-8.

A randomized, double-blind, placebo-controlled, crossover trial of an oral NK3R antagonist (MLE4901)



Women receiving an oral NK3R antagonist over a 4-week period had an overall 73% reduction in hot flush frequency (with a 45% reduction above placebo)

Lancet. 2017 May 6;389(10081):1809-1820.

Original Paper

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-endocrinology

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Neurokinin 3 Receptor Antagonism Reveals Roles for Neurokinin B in the Regulation of Gonadotropin Secretion and Hot Flashes in Postmenopausal Women

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Robert P. Millar[e, f] Richard A. Anderson[a]

Summary

- Progestin only systemic hormone therapy is effective to treat menopausal women with complications to estrogen.
- Oral progesterone is more effective than transdermal progesterone administration to improve VMS.
- Micronized progesterone is as effective as MPA to improve hot flush.
- Neurokinin receptor antagonist may be a potential treatment of choice for VMS of women who is contraindicated for HRT.

Thank you very much for your attention!!