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PROFESSOR

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Vietnam

VIETNAM - FRANCE - ASIA - PACIFIC
CONFERENCE ON OBSTETRICS AND GYNECOLOGY
Ho Chi Minh City, May 19th - 20th, 2016
16th

TREATMENT OF MENOPAUSE: HORMONAL and NON-HORMONAL THERAPY

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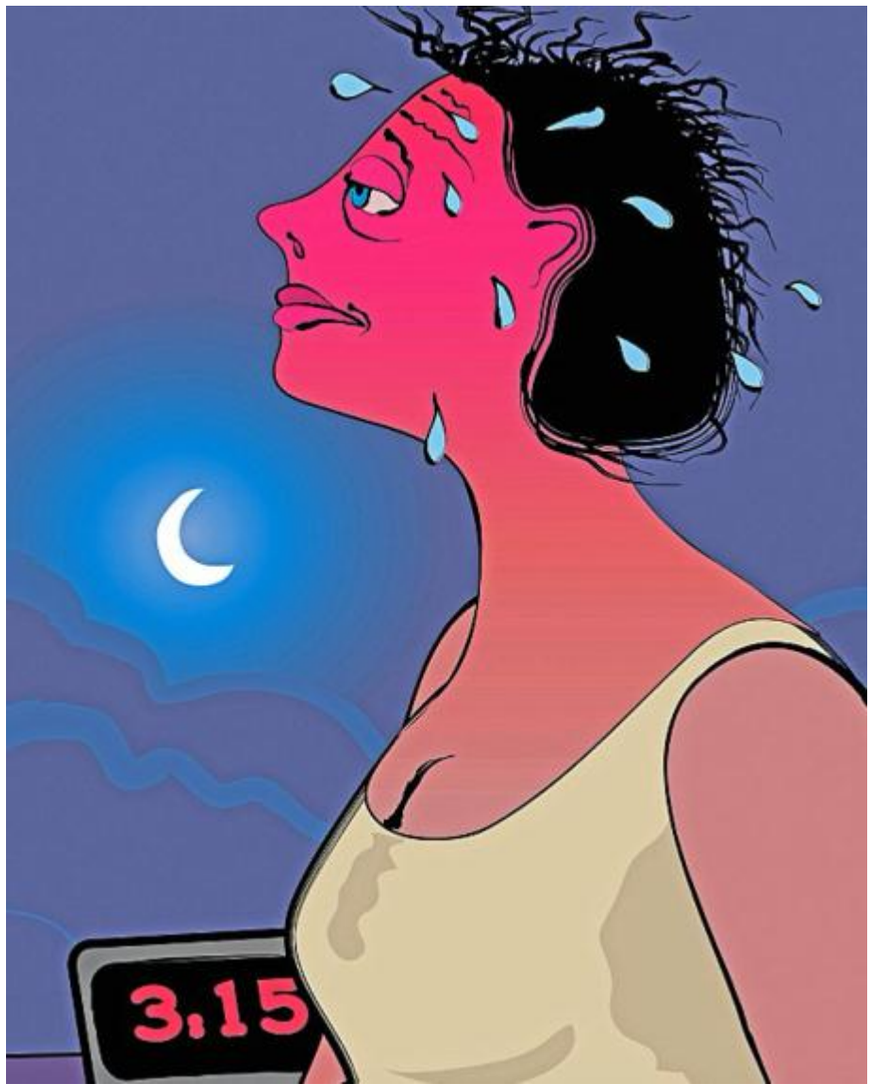
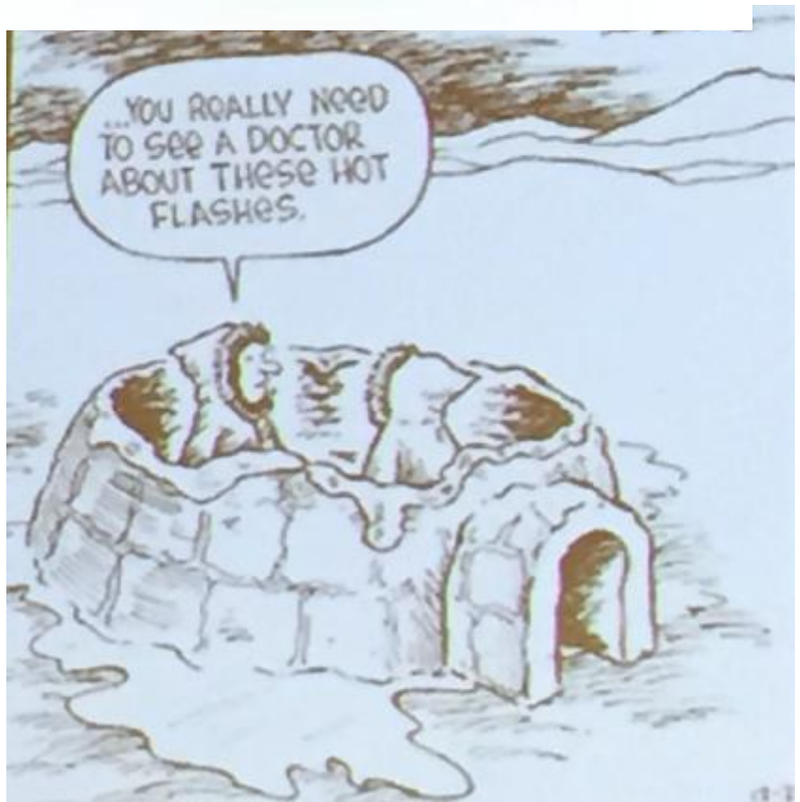
MHT – MENOPAUSE HORMONE THERAPY - A DECADE AFTER WHI

- WHI – Women' Health Initiative
- Published on July 2002
- Resulting in many negative effects – "shock" in attitudes and practices toward MHT
- Many limitations, bias and drawbacks of this research were revealed afterward
- Many well-designed and scientific have been induced after WHI, concentrated on: advantages – disadvantages, positive and negative effects, risks and side effects of MHT



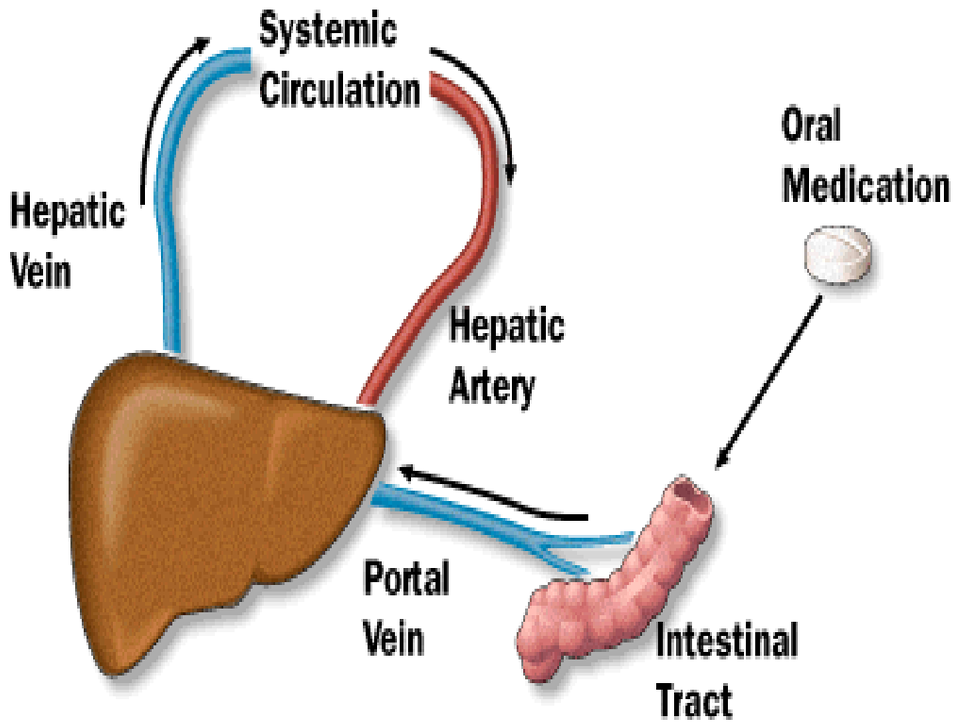
MHT, A DECADE AFTER WHI

- The benefits of MHT **outweighs** the risks when :
  - Indicated as soon as possible – perimenopause or within 10 years of menopause
  - Patient's age: not over 60 y/o
- MHT is an effective treatment for moderate to severe menopausal symptoms and may be one of the way for preventing osteoporosis, cardiovascular diseases and Alzheimer disease.



MHT, A DECADE AFTER WHI

- To women with premature ovarian failure: MHT is recommended at least until the age of natural menopause.
- Using MHT after 60 y/o or over 10 years of menopause : potential risks of MHT should be taken into account.
- Various routes for estrogen administration to consider: oral – transdermal – vaginal routes
- Oral administration: liver first-pass leads to increased embolism and decreased bioavailability => transvaginal / transdermal routes are more efficient



HRT, A DECADE AFTER WHI

- The optimal treatment duration for combined therapy (EPT) : 5 years without increased breast cancer risks.
- Estrogen – alone therapy: 7 years duration is safe.

MENOPAUSE HORMONE THERAPY

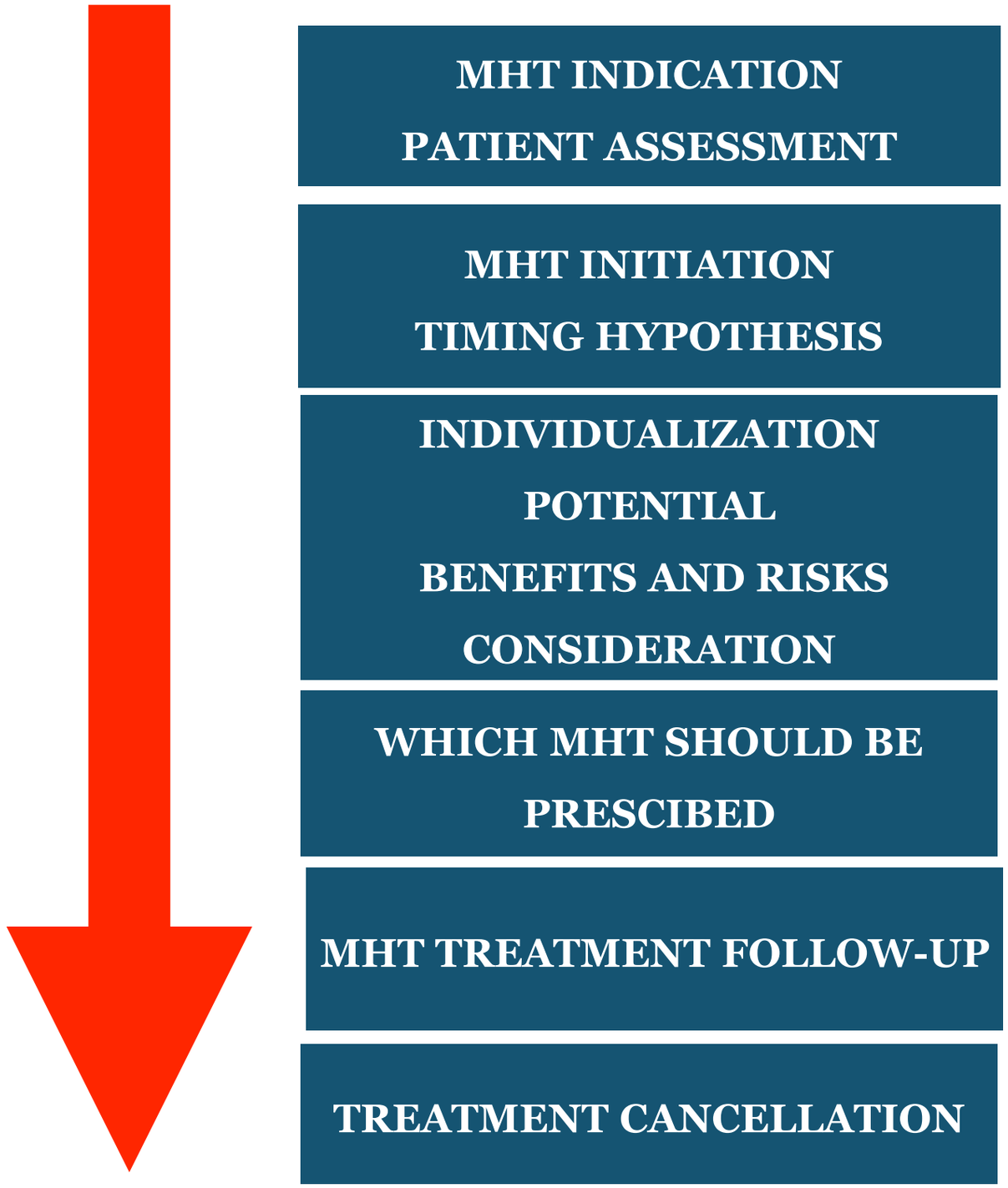
MENOPAUSE HORMONE THERAPY

- Systemic estrogen has been used more than half a century for the treatment of pre-menopausal disorders
- Many observational studies showed that MHT reduces cardiovascular morbidity = > RCTs conducted studies to verify : WHI and HERS
- Data from WHI and HERS: no effects for using MHT , but risks for stroke and coronary heart diseases increased

MENOPAUSE HORMONE THERAPY

- Re – analysis of WHI: unreasonable conclusions as the result of unsuitable population selection, inclusion criteria and incongruous treatment choice.
- KEEPS - the Kronos Early Estrogen Prevention Study: the timing hypothesis - “ the window of opportunity” where HRT may be beneficial for preventing CVD in younger women

MENOPAUSE HORMONE THERAPY



MENOPAUSE HORMONE THERAPY

MHT INDICATION
PATIENT ASSESSMENT

- Individual assessment
- Issues to be taken into account:

Family history

Patient's history

Patient's age

Age and health of her husband

The onset of menopause

Symptoms that the patient must suffer

BMI

Desires for her own future life

MHT INDICATION

PATIENT ASSESSMENT

Universal assessment:

- Gynaecologic and breast ultrasound
- Cancers screening
- Blood tests: total blood count,

fibrinogen, D-dimer, liver - kidney function tests

MHT INITIATION TIMING HYPOTHESIS

- **Most suitable time for MHT initiation:**

  * Under 60 y/o

  * Within 10 years after the onset of menopause

  → **Window of opportunity**

- **The initiation of MHT in women over 60: risks outweight benefits**

- Women with premature ovarian insuffficiency: MHT is recommended at least until the age of natural menopause, low dose OCP may be used.

MENOPAUSE HORMONE THERAPY

INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

Individual consideration should be noticed

- **Vasomotor symptoms**: MHT remains the most effective therapy
- **Osteoporosis:** MHT is a first-line therapy for the prevention of fracture in at-risk women before age 60 years or within 10 years after menopause, but not indicating solely for osteoporosis prevention.

MENOPAUSE HORMONE THERAPY

INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

Individual consideration should be noticed

- **Cardiovascular diseases:** For women < 60 and menopause <10 years, MHT has the potential for improving the cardiovascular risk profile through its beneficial effects on vascular function, cholesterol levels and glucose metabolism.

- **Coronary heart diseases**: young women, 50 - 59 y/o, or < 10 years from the onset of menopause, using MHT, have a trend of significant reduction in mortality and in hospitalization for myocardial infarction and congestive heart failure.

INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

- ***Stroke:*** depends on age – progestins – route of administration – current risk factors
  - Excess absolute risk of MHT lower among women < 60.
  - UK General practice research database: the risk of VTE and stroke is less with transdermal than with oral estradiol.
  - **Micronized progesterone and dydrogesterone associated with 17β-estradiol** may have a better risk profile.
  - MHT related with stroke in those who have current hypertension.
  - Women with premature ovarian failure: increased risk for stroke unless MHT is used.

INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

Breast cancer

- No increased risk in first-time users of MHT during the 5 - 7 years since initiation of treatment.
- WHI study: 7.1 years of treatment with unopposed CEE decreased the risk of breast cancer diagnosis and mortality in hysterectomized women.
- Risks are related to: time of the initiation – duration of administration – BMI.
- **Micronized progesterone or dydrogesterone** may be associated with a **better risk profile for breast cancer than synthetic progestogens.**
- The risk of breast cancer attributable to MHT is small and becomes normal after discontinuation of treatment.

INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

- **Venous thromboembolism**
  - ***A contra–indication for MHT***
  - Micronized progesterone or dydrogesterone may be associated with a better risk profile for VTE than synthetic progestogens.
  - Transdermal estrogen may avert some risk associated with oral MHT by avoiding first-pass hepatic metabolism.

INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

Urogyneacology

- Low- dose local estrogens are more preferable for atrophy or recurrent lower urinary tract infections management.
- Systemic risks have not been identified with local low-potency/low-dose and short - term estrogen treatment.
- Local estrogens within 12 months: no need for progestogen combination.

INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

Cognition

- MHT initiated around the time of menopause and/or in postmenopausal women < 60 is associated with a reduced risk of Alzheimer disease (29 - 44 % for young women, 50 - 59 years old, or < 10 years from the onset of menopause, bilateral oophorectomy)

- WHI: with respect to Alzheimer risk, starting MHT in later life is harmful.

- **Mood:** HRT is effective at alleviating short-term menopausal symptoms such as hot flashes, insomnia, mood swings, and irritability.

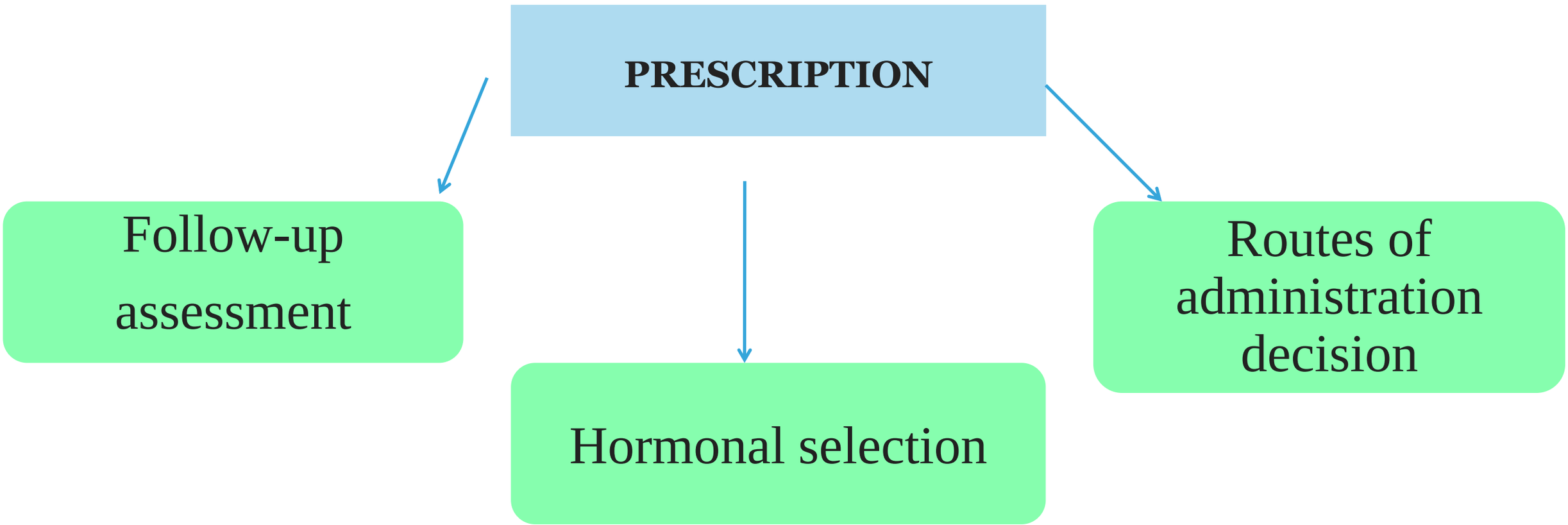
INDIVIDUALIZATION
POTENTIAL
BENEFITS AND RISKS
CONSIDERATION

Diabetes :

MHT is likely to decrease the serum glucose level. The mechanism, however, is not clear.

Insulin – resistance reduction is supposed to be the reason.

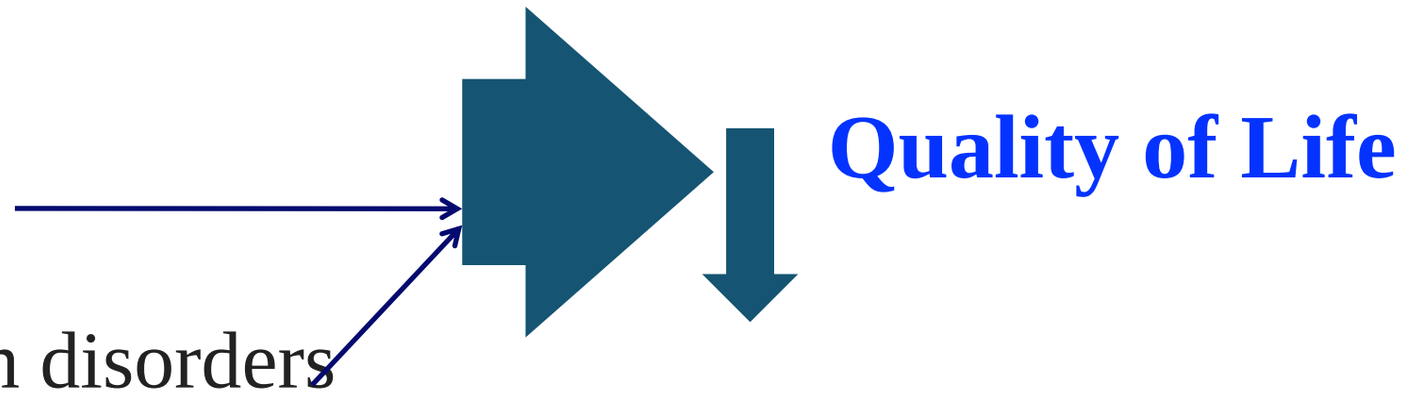
MENOPAUSE HORMONE THERAPY



ESTROGEN SELECTION

Hormonal selection

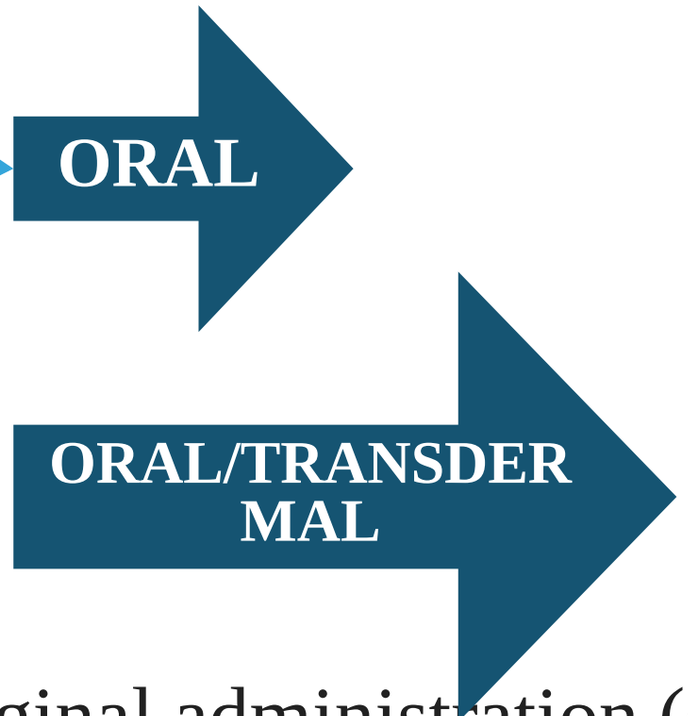
- **Decision for estrogen administration:**
  - Young age < 60 y/o, onset of menopause < 10 yrs (window of opportunity).
  - Vasomotor disorders
  - Autonomic nervous system disorders



- Estrogen must be asociated with progestin, if uterus intact
- Hysterectomy=> estrogen – alone therapy, except for :
  - Hysterectomy for endometrial cancer
  - Hysterectomy for endometriosis
  - Subtotal hysterectomy

Hormonal selection

- **Types of estrogen:**
  - Estradiol valeriate
  - CEE (Premarin)
  - 17β estradiol



- **Routes:** oral, transdermal and vaginal administration (estriol)

Hormonal selection and routes of administration

	Oral	Transdermal
Pharmakokinetics	**Fluctuating serum concentration**	**Relatively stable serum concentration**
Inflammatory index (C-reactive protein- CRP)	↑	**No effect**
Lipid metabolism	**Triglycerides và HDL ↑ LDL ↓**	**Triglycerides ↓ HDL và LDL No effect**
Hypertension	↑	↓
Insulin-like growth factor 1 (ILGF-1)	↓	**No effect**
Sex hormone-binding globulin (SHBG)	↑↑↑	↑
Embolism protein	↑	**No effect**

PROGESTOGEN SELECTION

Hormonal selection

- Progestogen combined with systemic estrogen for endometrial hyperplasia and cancer prevention
- Sequential or 12 – 14 days/ cycle
- Origin: natural or sub-natural
  - Natural origin: progesterone
  - Semisynthesis: micronized progesterone, dydrogesterone
  - Synthesis

Hormonal selection

- ***Progestogen and risk of breast cancer***

- WHI: a breast cancer risk **reduction with conjugated equine estrogens (CEE) alone** and a risk elevation with CEE plus medroxyprogesterone acetate (CEE + MPA) were observed

- **KEEPS**:
  - KEEPS: HT in recently menopausal women is not associated with serious adverse effects in the first four years of use

    Group 1: micronized progesterone + transdermal 17β-estradiol

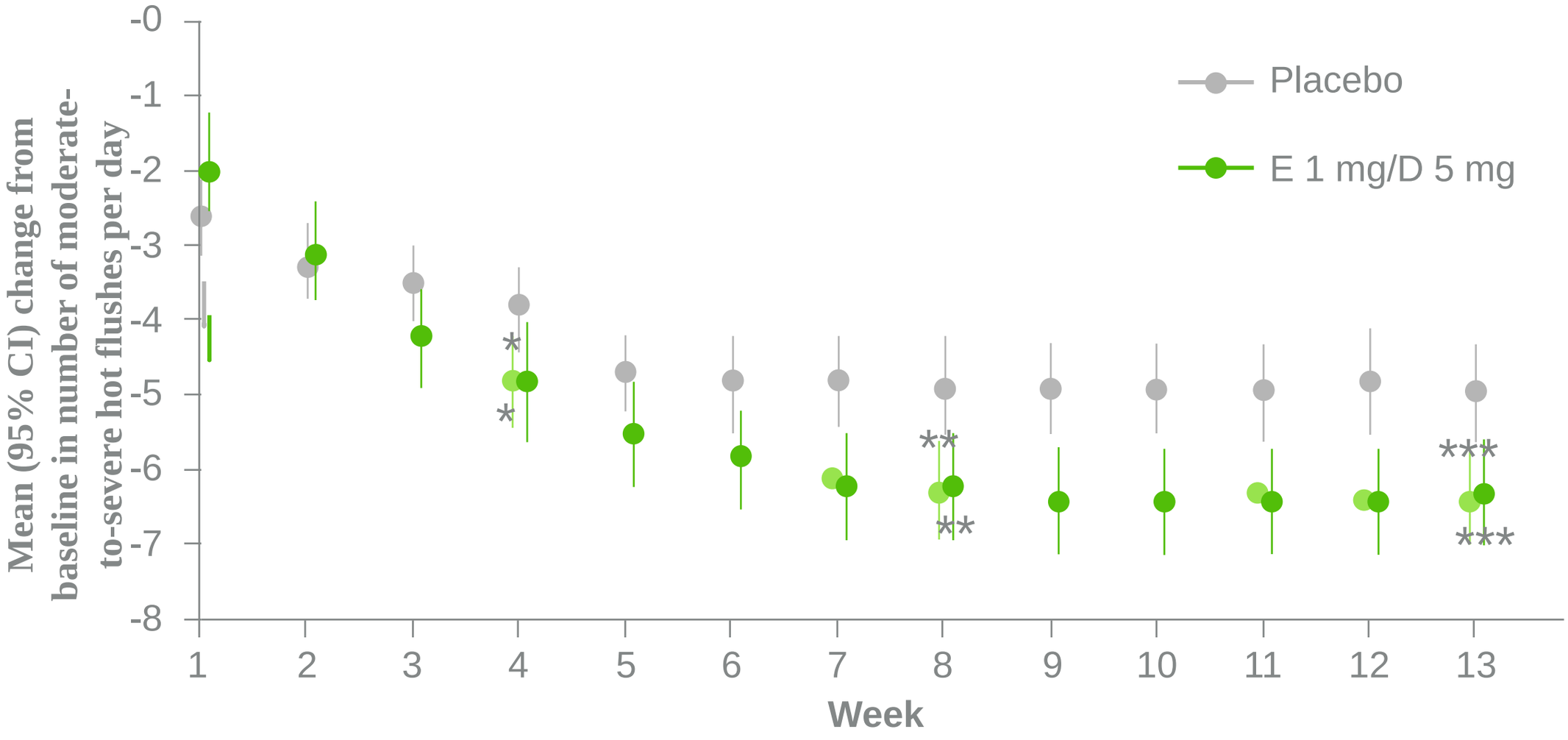
    Group 2: micronized progesterone + CEE

    Group 3 : placebo

No increase for breast cancer risks observed

ORAL LOW-DOSE CONTINUOUS E2 0.5 MG/D 2.5 MG EFFECTIVELY ALLEVIATE VASOMOTOR SYMPTOMS

Reduction of symptoms significantly different between 2 groups; n= 305

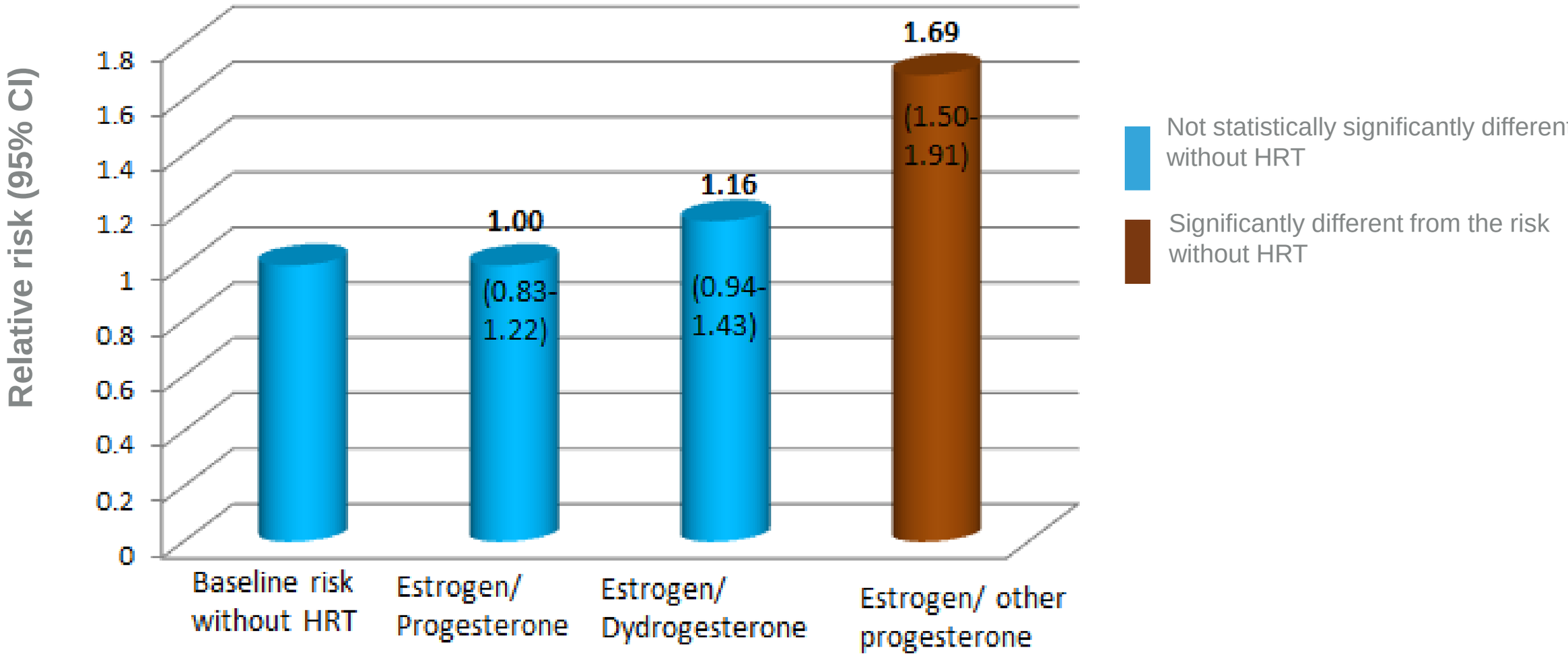


*p<0.05, **p<0.01, ***p<0.001 vs. placebo

Figure reproduced from Maturitas, 67, Stevenson JC et al. Oral ultra-low dose continuous combined hormone replacement therapy with 0.5mg 17β-oestradiol and 2.5mg dydrogesterone for the treatment of vasomotor symptoms: Results from a double-blind, controlled study. 227–32, Copyright (2010), with permission from Elsevier.

BREAST CANCER RISKS ACCORDING TO PROGESTOGEN CHOICE

FRENCH E3N COHORT STUDY

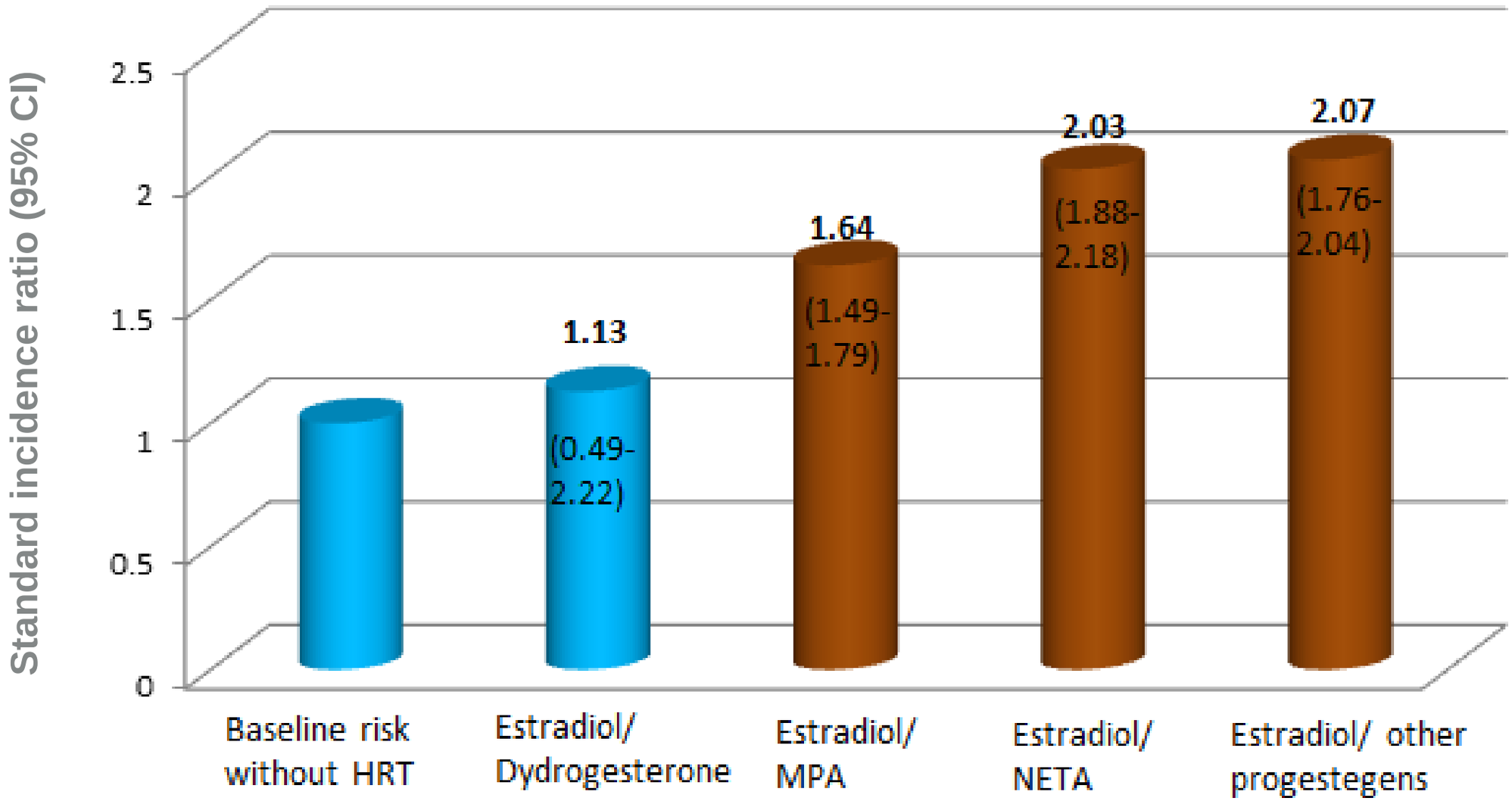


N = 80,377 women, for an average treatment duration of 8.1 years

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

BREAST CANCER RISKS ACCORDING TO PROGESTOGEN CHOICE

FINNISH COHORT STUDY



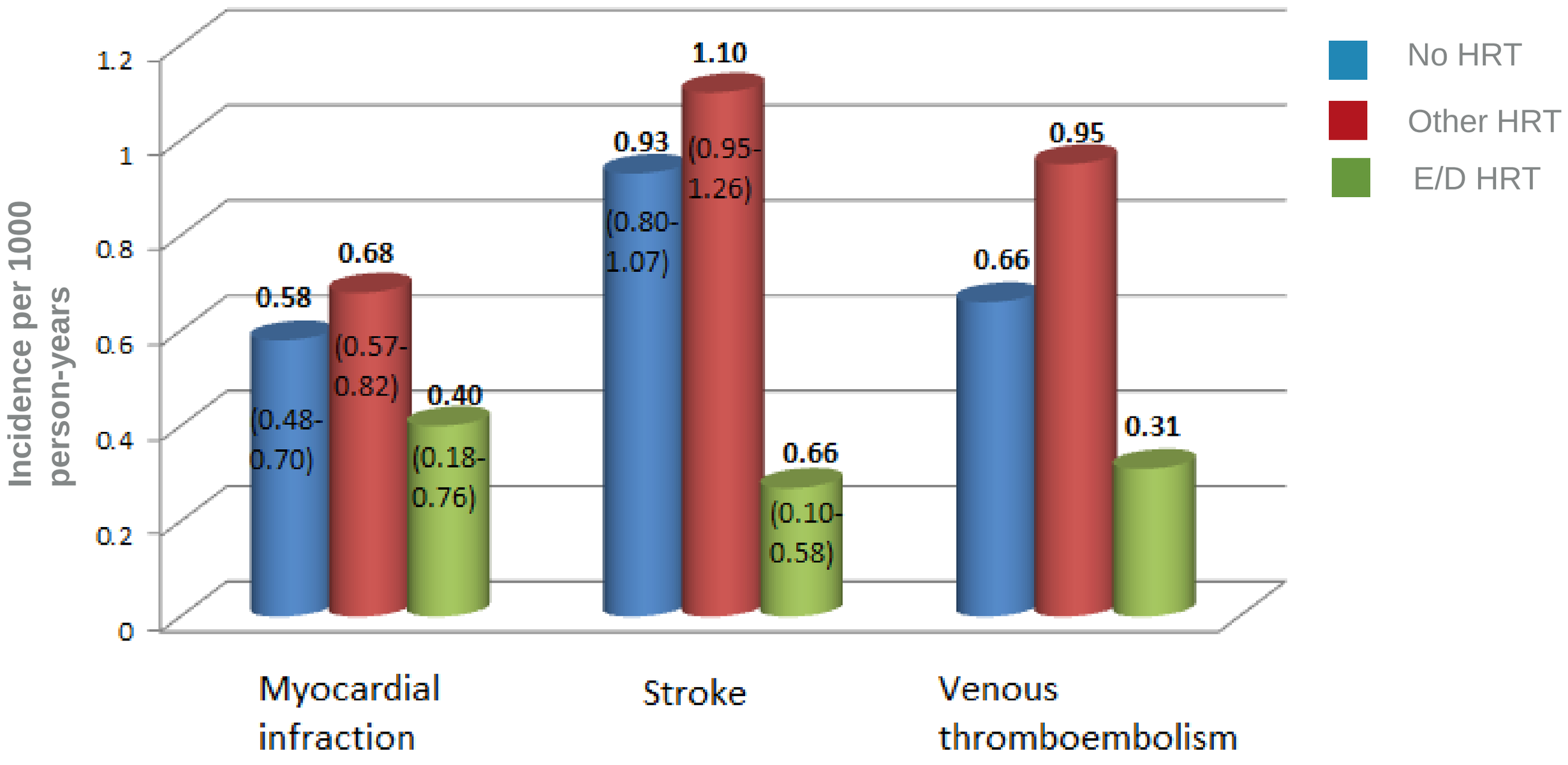
N = 50,210; women >50 years of age; treatment duration 5 years

 Lyytinen H et al. Obst Gyn 2009;113:65–73.

ESTRADIOL/DYDROGESTERONE REDUCE THE CARDIOVASCULAR RISKS

- Population study based on UK-based General Practice Research Data (n=69,412)
- 6 years follow-up
- No increase in cardiovascular events when taking E/D

ESTRADIOL/DYDROGESTERONE REDUCE THE CARDIOVASCULAR RISKS

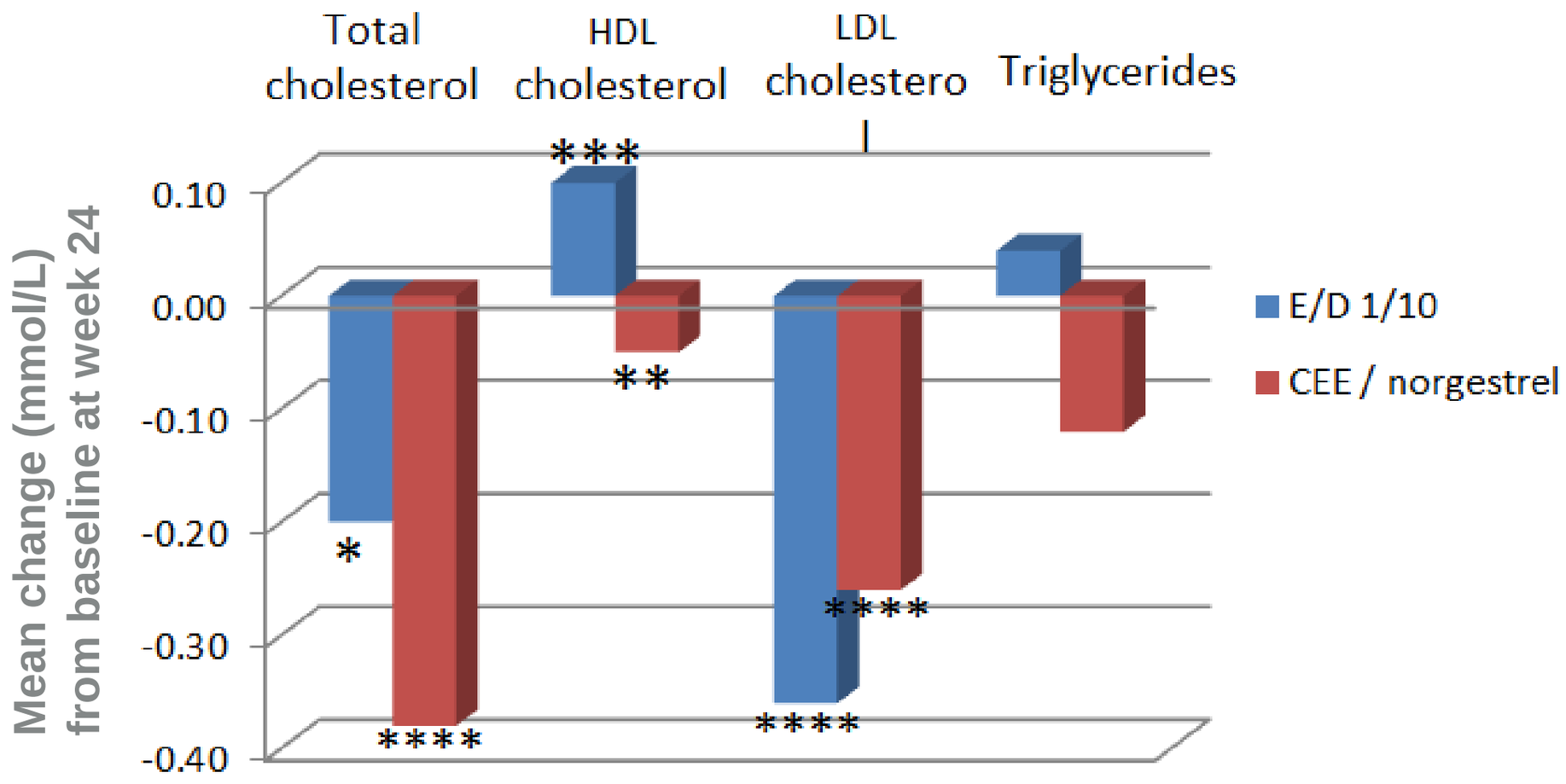


- Schneider C et al. Climacteric 2009;12:445–53.

LIPID PROFILE
ESTRADIOL/DYDROGESTERONE VS. CEE/NORGESTREL

In a 24 weeks – study on 193 women at peri- or post- menopausal age:

- HDL significantly increased with E/D
- HDL decreased with CEE/norgestrel (0.625/0.15 mg)

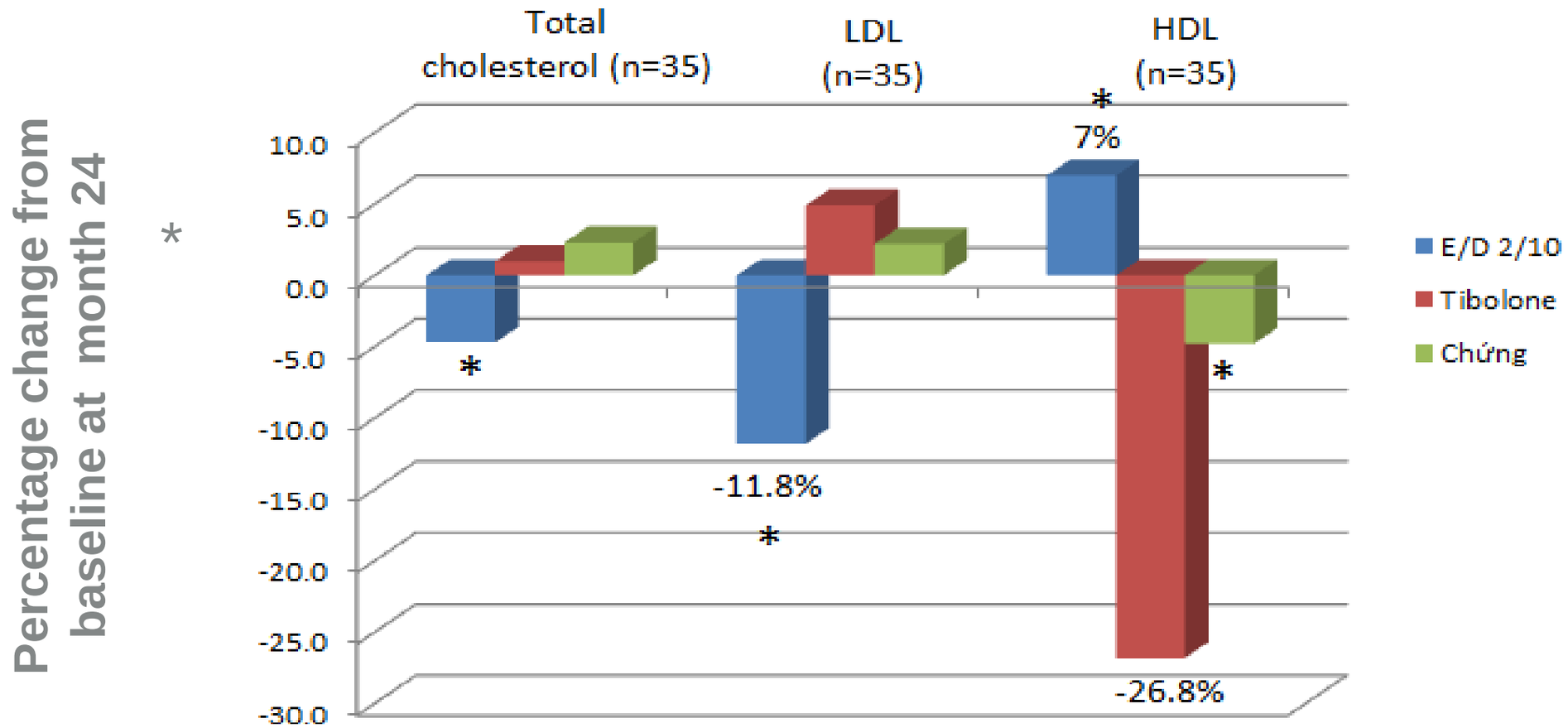


*p=0.05, **p=0.01, ***p=0.003, ****p=0.001 vs. baseline

Cieraad D et al. Arch Gynecol Obstet 2006;274:74–80.

LIPID PROFILE
ESTRADIOL/DYDROGESTERONE VS TIBOLONE

A further study on 140 healthy, postmenopausal women to evaluate the effects of sequential E/D on lipid profile after 24 months. E/D 2/10 group: significantly increased in mean HDL- cholesterol 7% in comparision with decrease in mean 26.8% HDL cholesterol in tibolone group

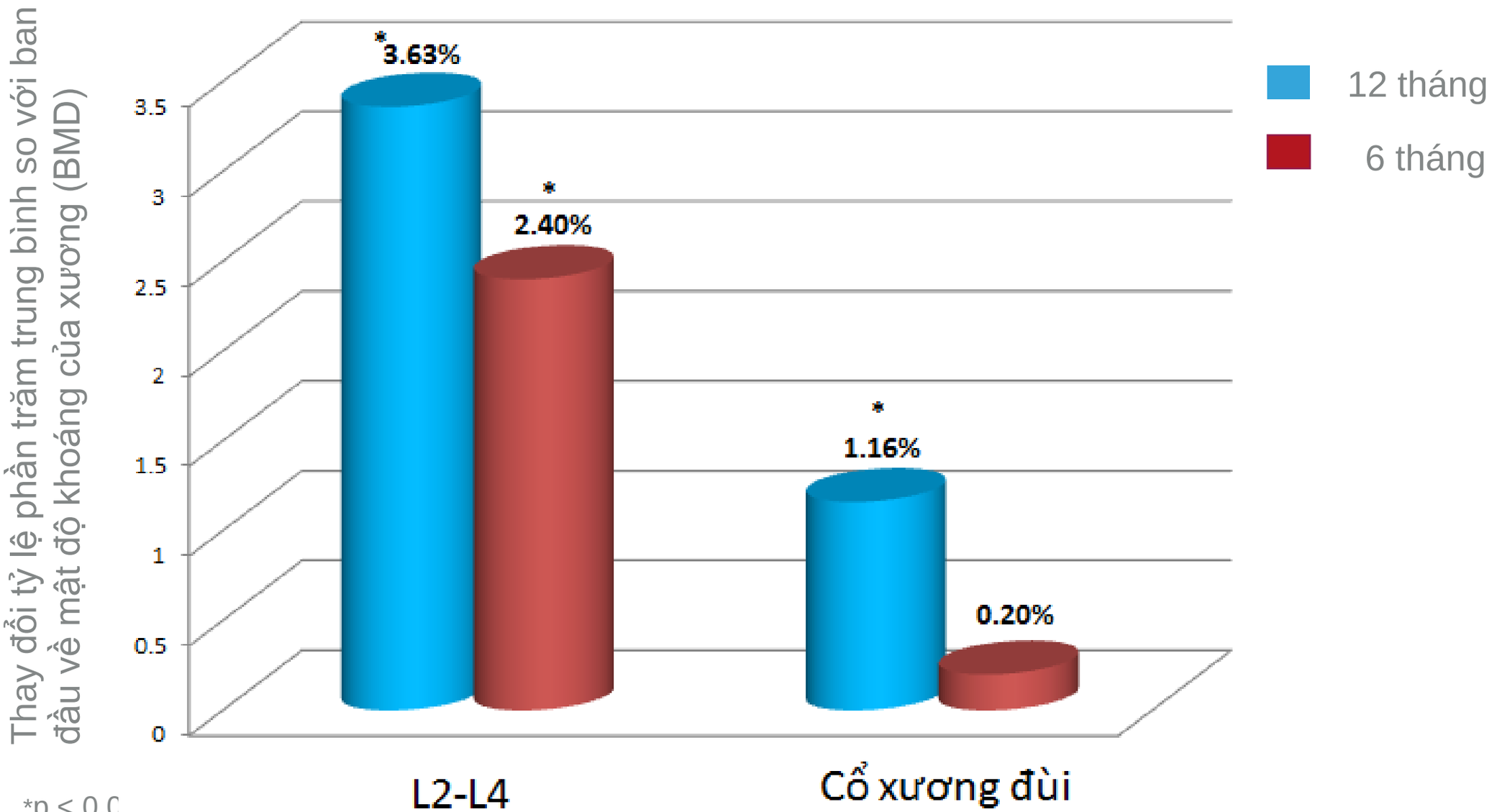


*p<0.05 vs. baseline

Hänggi W et al. Brit J Obst Gyn 1997;104:708–17.

BENIFICIAL EFFECTS OF CONTINUOUS ESTRADIOL/DYDROGESTERONE IN IMPROVING THE BONE MINERAL DENSITY (BMD)

- 1/5, 1/10 và 1/20 E/D continuous significantly increased BMD of lumbar spines and hip (n=214)



*p < 0,C

Stevenson J và cộng sự. Maturitas 2001;38:197–203.

Follow-up assessment

- ***First follow-up visit:***
  - Drug absorption and interaction?
  - Symptoms improvement
  - Side-effects?
  - Switching (d osage - routes)?
- **Re – assessment every 6 months – 1 year, including:**
  - Physical and gynecologic check-up,
  - Ultrasound (gynecology and breast); mammography; bone density assessment; blood tests (total blood count, liver and kidney functions); cancer screening tests; review and discussion of individual's risk:benefit ratio concerning MHTon every time check-up.

MHT DISCONTINUATION

- Duration: 5 yrs for combined therapy, 7 yrs for estrogen – alone therapy
- Special cases:
  - Premature ovarian failure: low-dose OCs until the natural menopause age.
  - ***Osteoporosis prevention, bisphosphonate intolerance***: MHT used for over 5 – 7 years => discussion with patient.
- Withdrawal: suddenly/ gradually; symptoms recur among 50% of patients => MHT or non-hormonal therapy consideration.
- **IMS congress 2015 (4-6 December 2015 in Taipei)** : whether MHT should be stopped if it is being used effectively, without any side-effects for a duration of 5 -7 years?

NON-HORMONAL THERAPY

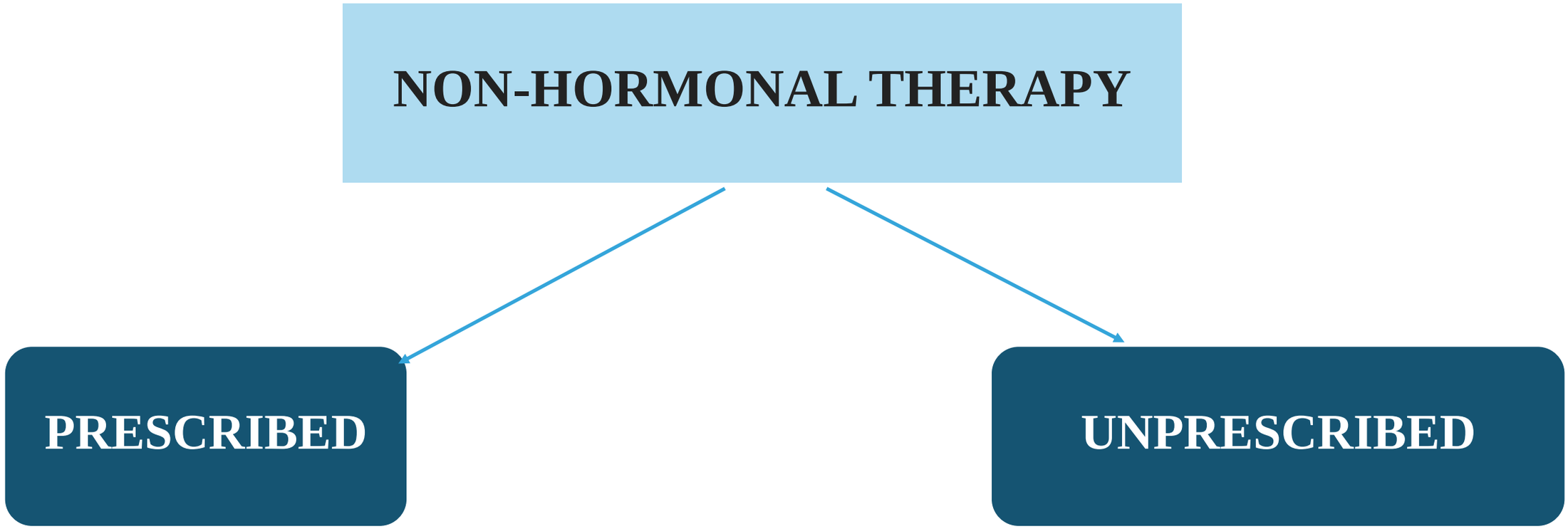
NON-HORMONAL THERAPY

- Shock caused by the release of the principal results of the WHI led to the sharp fall of the number of women taking MHT :

- Germany: **40,2**% (2003 – 2004 vs 1997 – 1999) (Du et al.,2007)
- Australia: **55% in women aged** 50 – 80 y/o (2003 vs 2001) (Travers et al., 2006)
- USA: **77%** of starting MHT in women aged 50 – 79 y/o (2004 vs 2001) (Weglenka et al., 2006).

APPEARANCE OF NON-HORMONAL AGENTS

NON-HORMONAL THERAPY



UNPRESCRIBED THERAPY

LIFESTYLE MODIFICATION

- Increasing physical activities
- Reducing body weight
- Healthy diet and functional supplements
- Meditation, deep breathing intermittent, relaxing
- Hypnosis

FUNCTIONAL SUPPLEMENTS

- Soya and products with soya origins
- Dong quai and black cohosh
- Vitamin E
- Omega-3
- Vitamin D3

UNPRESCIBED THERAPY

FUNCTIONAL SUPPLEMENTS:

Maca is a plant that grows in central Peru in the high plateaus of the Andes Mountains. It has been cultivated as a vegetable crop in this area for at least 3000 years.

Maca is a relative of the radish and has an odor similar to butterscotch. Its root is used to make medicine.

Maca also appears to be a potent suppressor of prostate hypertrophy, with potency similar to finasteride, a synthetic drug for the treatment of enlarged prostates. Preliminary research also suggests that maca can protect the brain from damage, improve bone health, and even improve cognitive ability in healthy people.

(IMS Congress 2015; 4-6/12 in Taipei)

PRESCRIBED THERAPY

- Paraxetine.
- Selective Serotonin Reuptake inhibitors (SSRI) & Serotonin-Norepinephrine Reuptake inhibitors (SNRI).
- Gabapentinoids
- Clonidine

OTHER THERAPY

- Acupuncture
- Stellate ganglion block

CONCLUSION

- **Women, who experience spontaneous or iatrogenic menopause and suffer severe vasomotor symptoms, should use MHT after universal assessment to reduce symptoms and maintain quality of life.**
- **Duration for MHT administration depends on the purposes when indicated.**
- **To women with premature ovarian insufficiency: MHT is recommended at least until the age of natural menopause.**
- **Women with mild symptoms or treatment completion: non – hormonal therapy may be an alternative.**

CONCLUSION

- **Issues to be considered when indicating MHT for patients:**
  - **Window of opportunity**
  - **Patients' history**
  - **Risks for thromboembolic events**
  - **Estrogen and progestin selection: The combination of 17β-estradiol & dydrogesterone was proven not increase breast cancer – venous thromboembolism and stroke risks.**
  - **Patients should be counseled carefully about the potential benefits – risks and result of the treatment each visit for follow-up assessment**
- **Lifestyle modifications include socializing and being physically/mentally active; healthy diets; weight loss of 5 -10% prove quality of life and ensure a healthy menopause.**

Thanks for your attention

REFERENCE

1. Lobo RA. Where are we 10 years after the Women's Health Initiative? J Clin Endocrinol Metab. 2013;98(5):1771–1780.

2. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004;291(1):47–53.

3. Hodis HN, Collins P, Mack WJ, Schierbeck LL. The timing hypothesis for coronary heart disease prevention with hormone therapy: past, present and future in perspective. Climacteric. 2012;15(3):217–228.

4. North American Menopause Society The 2012 hormone therapy position statement of The North American Menopause Society. Menopause. 2012;19(3):257–271.

5. Panay N, Hamoda H, Arya R, Savvas M, British Menopause Society, Women's Health Concern The 2013 British Menopause Society and Women's Health Concern recommendations on hormone replacement therapy. Menopause Int. 2013;19(2):59–68.

6. de Villiers TJ, Pines A, Panay N, et al. Updated 2103 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric. 2013;16:316–337.

7. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health. 2006;96(7):1226–1235.

8. Woods NF, Mitchell ES. Sleep symptoms during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. Sleep. 2010;33(4):539–549.

9. Freeman EW. Associations of depression with the transition to menopause. Menopause. 2010;17(4):823–827.

10. Lamont J. Female sexual health consensus clinical guidelines. J Obstet Gynaecol Can. 2012;34(8):769–775.

REFERENCE

11. Gregersen N, Jensen PT, Giraldi AE. Sexual dysfunction in the peri- and postmenopause. Status of incidence, pharmacological treatment and possible risks. A secondary publication. Dan Med Bull. 2006;53(3):349–353.

12. NIH State-of-the-Science Conference Statement on management of menopause-related symptoms. NIH Consens State Sci Statements. 2005;22(1):1–38. [No authors listed]

13. Shuster LT, Rhodes DR, Gostout BS, et al. Premature menopause or early menopause: long-term health consequences. Maturitas. 2009;65(2):161–166.

14. Hodis HN, Mack WJ. Hormone replacement therapy and the association with coronary heart disease and overall mortality: clinical application of the timing hypothesis. J Steroid Biochem Mol Biol. July2013 [Epub ahead of print.]

15. Clarkson TB, Melendez GC, Appt SE. Timing hypothesis for post-menopausal hormone therapy: its origin, current status, and future. Menopause. 2013;20(3):342–353.

16. Maki P. Is timing everything? New insights into why the effect of estrogen therapy on memory might be age dependent. Endocrinology. 2013;154(8):2570–2572.

17. Daniel JM. Estrogens, estrogen receptors, and female cognitive aging: the impact of timing. Horm Behav. 2013;63(2):231–237.

18. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297(13):1465–1477.

19. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women’s Health Initiative randomized trial. JAMA. 2003;290(13):1729–1738.

20. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354(7):669–683.

REFERENCE

21. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia. 2004;47(7):1175–1187.

22. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2003;138(1):1–9.

23. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy post-menopausal women: the Women's Health Initiative randomized trial. JAMA. 2003;289(24):3243–3253.

24. Simon JA. What's new in hormone replacement therapy: focus on transdermal estradiol and micronized progesterone. Climacteric. 2012;15(Suppl 1):3–10.

25. de Villiers TJ, Gass ML, Haines CJ, et al. Global Consensus Statement on menopausal hormone therapy. Maturitas. 2013;74(4):391–392.

26. Stuenkel CA, Gass ML, Manson JE, et al. A decade after the Women's Health Initiative – the experts do agree. Fertil Steril. 2012;98(2):313–314.

27. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2010;95(7 Suppl 1):s1–s66.

28. Valdiviezo C, Lawson S, Ouyang P. An update on menopausal hormone replacement therapy in women and cardiovascular disease. Curr Opin Endocrinol Diabetes Obes. 2013;20(2):148–155.

29. Sites CK, L'Hommedieu GD, Toth MJ, Brochu M, Cooper BC, Fairhurst PA. The effect of hormone replacement therapy on body composition, body fat distribution, and insulin sensitivity in menopausal women: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2005;90(5):2701–2707.

30. Zhu L, Brown WC, Cai Q, et al. Estrogen treatment after ovariectomy protects against fatty liver and may improve pathway-selective insulin resistance. Diabetes. 2013;62(2):424–434.

REFERENCE

31. Henderson VW, Lobo RA. Hormone therapy and the risk of stroke: perspectives 10 years after the Women's Health Initiative trials. Climacteric. 2012;15(3):229–234.

32. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA. 2011;305(13):1305–1314.

33. Rocca WA, Grossardt BR, Miller VM, Shuster LT, Brown RD., Jr Premature menopause or early menopause and risk of ischemic stroke. Menopause. 2012;19(3):272–277.

34. Rivera CM, Grossardt BR, Rhodes DJ, Rocca WA. Increased mortality for neurological and mental diseases following early bilateral oophorectomy. Neuroepidemiology. 2009;33(1):32–40.

35. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol. 2009;113(5):1027–1037.

36. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. BMJ. 2010;340:c2519.

37. Løkkegaard E, Jovanovic Z, Heitmann BL, et al. Increased risk of stroke in hypertensive women using hormone therapy: analyses based on the Danish Nurse Study. Arch Neurol. 2003;60(10):1379–1384.

38. Stefanick ML, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA. 2006;295(14):1647–1657.

39. Beral V, Million Women Study Collaborators Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003;362(9382):419–427.

40. Beral V, Reeves G, Bull D, Green J. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst. 2011;103(4):296–305.

REFERENCE

41. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med. 1995;332(24):1589–1593.

42. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol. 2000;152(10):950–964.

43. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. Arch Intern Med. 2006;166(9):1027–1032.

44. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840–845.

45. Scarabin PY, Oger E, Plu-Bureau G, EStrogen and THromboEmbolism Risk Study Group Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet. 2003;362(9382):428–432.

46. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in post-menopausal women: systematic review and meta-analysis. BMJ. 2008;336(7655):1227–1231.

47. Laliberte F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. Menopause. 2011;18(10):1052–1059. [PubMed]

48. Maki PM. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause. 2013;20(6):695–709.

49. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity. Brain Res. 2011;1379:188–198.

50. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology. 1988;13(4):345–357.

REFERENCE

51. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003;289(20):2651–2662.

52. Soares CN. Can depression be a menopause-associated risk? BMC Med. 2010;8:79.

53. MacBride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clin Proc. 2010;85(1):87–94.

54. North American Menopause Society The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause. 2007;14(3 Pt 1):355–369.

55. Simon JA, Kokot-Kierepa M, Goldstein J, Nappi RE. Vaginal health in the United States: results from the Vaginal Health: Insights, Views and Attitudes survey. Menopause. 2013;20(10):1043–1048.

56. Sturdee DW, Panay N, International Menopause Society Writing Group Recommendations for the management of postmenopausal vaginal atrophy. Climacteric. 2010;13(6):509–522.

57. Simon JA, Maamari RV. Ultra-low-dose vaginal estrogen tablets for the treatment of postmenopausal vaginal atrophy. Climacteric. 2013;16(Suppl 1):37–43.

58. Cody JD, Richardson K, Moehrer B, Hextall A, Glazener CM. Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev. 2009;4:CD001405.

59. Shapiro S, Kelly JP, Rosenberg L, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med. 1985;313(16):969–972.

60. AlHilli MM, Hopkins MR, Famuyide AO. Endometrial cancer after endometrial ablation: systematic review of medical literature. J Minim Invasive Gynecol. 2011;18(3):393–400.

REFERENCE

61. Crandall C. Low-dose estrogen therapy for menopausal women: a review of efficacy and safety. J Womens Health (Larchmt) 2003;12(8):723–747.

62. Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: a review. Menopause. 2004;11(3):356–367.

63. Sood R, Shuster L, Smith R, Vincent A, Jatoi A. Counseling postmenopausal women about bioidentical hormones: ten discussion points for practicing physicians. J Am Board Fam Med. 2011;24(2):202–210.

64. Goodman MP. Are all estrogens created equal? A review of oral vs transdermal therapy. J Womens Health (Larchmt) 2012;21(2):161–169.

65. Arlt W. Androgen therapy in women. Eur J Endocrinol. 2006;154(1):1–11.

66. Minkin MJ. Considerations in the choice of oral vs transdermal hormone therapy: a review. J Reprod Med. 2004;49(4):311–320.

67. Fitzpatrick LA, Good A. Micronized progesterone: clinical indications and comparison with current treatments. Fertil Steril. 1999;72(3):389–397.

68. Barrett-Connor E, Slone S, Greendale G, et al. The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women. Maturitas. 1997;27(3):261–274.

69. Montplaisir J, Lorrain J, Denesle R, Petit D. Sleep in menopause: differential effects of two forms of hormone replacement therapy. Menopause. 2001;8(1):10–16.

70. de Lignieres B. Oral micronized progesterone. Clin Ther. 1999;21(1):41–60.

REFERENCE

71. Sitruk-Ware R, Bricaire C, De Lignieres B, Yaneva H, Mauvais-Jarvis P. Oral micronized progesterone. Bioavailability pharmacokinetics, pharmacological and therapeutic implications – a review. Contraception. 1987;36(4):373–402.

72. The North American Menopause Society KEEPS Results Give New Insight Into Hormone Therapy. 2012. [Accessed October 5, 2013]. Available from: http://www.menopause.org/annual-meetings/2012-meeting/keeps-report.

73. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107(1):103–111.

74. de Ziegler D, Ferriani R, Moraes LA, Bulletti C. Vaginal progesterone in menopause: Crinone 4% in cyclical and constant combined regimens. Hum Reprod. 2000;15(Suppl 1):149–158.

75. Lewis JG, McGill H, Patton VM, Elder PA. Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women. Maturitas. 2002;41(1):1–6.

76. Sitruk-Ware R. The levonorgestrel intrauterine system for use in peri- and postmenopausal women. Contraception. 2007;75(Suppl 6):S155–S160.

77. Haimov-Kochman R, Barak-Glantz E, Arbel R, et al. Gradual discontinuation of hormone therapy does not prevent the reappearance of climacteric symptoms: a randomized prospective study. Menopause. 2006;13(3):370–376.

78. Mikkola TS, Clarkson TB, Notelovitz M. Postmenopausal hormone therapy before and after the Women's Health Initiative study: what consequences? Ann Med. 2004;36(6):402–413.

79. Santen RJ, Allred Dc, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2010 Jul;95(7 Suppl 1):s1–s66. doi: 10.1210/jc.2009-2509. Epub Jun 21, 2010.

80. The North American Menopause Society (menopause.org) [homepage on the Internet] Hormone Products for Postmenopausal Use in the United States and Canada. [Accessed December 11, 2013].

81. Richa Sood, Stephanie S Faubion, Carol L Kuhle, Jacqueline M Thielen, and Lynne T Shuster. *Prescribing menopausal hormone therapy: an evidence-based approach.* Int J Women's Health, 2014;6:47-57. Published online 2014 Jan, doi: 10.2147/IJWH.S38342.

82. *Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society*. The Journal of The North American Menopause Society. Vol 22 N0 11 pp. 000-000. DOI: 10.1097/GNE.0000000000000546 © 2015 by The North American Menopause Society.